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I

THE PITUITARY

A STUDY OF THE MORPHOLOGY, PHYSIOLOGY, PATHOLOGY, AND SURGICAL TREATMENT OF THE PITUITARY, TOGETHER WITH AN ACCOUNT OF THE THERAPEUTICAL USES OF THE EXTRACTS MADE FROM THIS ORGAN

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TO

MY FRIEND

J. ARTHUR SMITH

PREFACE

In this monograph an attempt has been made to describe and discuss within a reasonable compass our present knowledge with regard to the Pituitary Body, in the belief that a more or less complete summary of the subject is needed by the clinician, if not by the morphologist and physiologist, owing to the commanding position this organ now occupies in Medicine, Surgery, and Gynæcology, as well as in the other specialities. Descriptions of the Pituitary are to be found in various monographs, such as those of Thaon, Fischer, and Cushing, and in the works on the internal secretions of Biedl, Vincent and others ; but in one aspect or another these accounts appear to lack the completeness, manner of presentation, or point of view that is required by the general reader, however well they fulfil special requirements.

Our own experimental work—commenced in 1906—was primarily undertaken in order to elucidate the relationship of the Pituitary to the female genital functions, and to determine the physiological and therapeutical importance of extracts made from this organ ; but we were led in our investigations further afield, for it was difficult to study comprehensively such special aspects as those mentioned without first obtaining an intimate knowledge of the morphology, and, so far as possible, of the pathology of the organ in question. Thus it came about that a considerable amount of material and information was collected from the work of others, and also as the result of our own observations. Our researches have been concerned with the histological anatomy from developmental, physiological and comparative points of view ; with the physiological actions of the extracts, the interrelationships between the Pituitary and other organs of internal secretion, the effects of partial and complete removals, the results of experimentally produced infections, the general pathology, and with the therapeutical uses of extracts of the

Pituitary. It is the information and material so obtained that form the subject-matter of this volume.

It would be impossible, of course, completely to discuss all the work that has been done in regard to the Pituitary—to do so would mean a compilation of many volumes containing much confirmatory and contradictory evidence. Only the more essential particulars, therefore, have been given; for at the present time a critical study of the accuracy of our acquired information and an attempt to correlate our knowledge is probably more needed than a mere string of statements. For the same reason a comprehensive bibliography of the subject has not been attempted, but numerous references to statements quoted and investigations mentioned are given.

In these circumstances it is possible that valuable work of others has escaped attention, and that our own less important investigations have been given undue prominence. If so, it may be pointed out that this book is not intended to be a mere compilation, but, rather, the presentation of an attempt to study the Pituitary from every point of view.

Some of the original work contained in the following pages has been published previously; and it includes that for which the author was awarded the John Hunter Medal and the Triennial Prize by the Council of the Royal College of Surgeons, England, and the Astley Cooper Prize, as well as the substance of a Hunterian Lecture delivered at the Royal College of Surgeons.

In addition to my obligation to Mr. Arthur Smith, who has defrayed the laboratory expenses in connexion with my researches, and to whom this work is inscribed, I am indebted to my colleagues Professor J. A. McDonald and Professor E. E. Glynn for laboratory facilities. Miss Miriam Alderson has given me much valuable assistance, especially in regard to the references and in the compilation of the index. My laboratory assistant—now Private Walter Plevin, R.A.M.C.—has drawn many of the illustrations other than the photographs. Private Fred Holliday, also, has been responsible for some of the pictures. Owing to the difficulty of securing artistic assistance after they had left, a number of photomicrographs have been reproduced; and at the last moment Miss E. M. Wright kindly drew a few illustrations. All the photographs and drawings, other than those indicated, have been made from my own material.

As this work has been produced at a time of great stress and difficulty, some allowance must be made for imperfections that may be found in regard to publication and authorship. I must, however, thank Mr. W. A. Clowes of Messrs. William Clowes and Sons for the personal interest he has taken in the printing of the book, and Dr. Hubert Armstrong for reading the proofs.

W. B. B.

38, Rodney Street,
Liverpool,
November, 1918.

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INTRODUCTION

After many centuries spent in unprofitable speculation and fruitless investigation, the far-reaching—the vital—importance of the Pituitary has at last come to be fully recognized.

To those who have made a study of the history of the subject the extraordinary vicissitudes that have accompanied the acquisition of our knowledge of the Pituitary Body, and the strange lapses into oblivion when recognition of its importance seemed within our grasp, are almost incredible. For ages a subject of curiosity and of strange beliefs—as witness the very name, derived from *pituita*, meaning phlegm, which by Galen and other ancient writers it was supposed to secrete into the nasal cavity[1]—this structure is now the object of the keenest scientific interest.

The Pituitary Body is an organ of internal secretion, and is, as we shall see later, of vital importance to the animal organism.

The phenomenon of internal secretion, or hormonopoiesis, is fully recognized in regard to many individual hormonopoietic organs; but the problem of the correlation of the internal secretions of the coordinated system of hormonopoietic organs, of which the Pituitary forms a part, is very complicated, and for the most part imperfectly understood, although it is now acknowledged by most authorities that this correlation is a close one, and that the influence of any one of the hormonopoietic organs on the metabolism cannot be completely considered apart from the interaction of the rest.

[1] Vieussens, Sylvius, and other ancient writers considered that the Pituitary was concerned in the formation of the cerebrospinal fluid. Commenting on this view Cushing calls attention to the fact that cerebrospinal fluid, which, following Herring, he thinks receives secretion directly from the Pituitary, may in certain pathological circumstances escape from the nose.

Richard Lower, in a tract (*Dissertatio de Origine Catarrhi*) published in 1672, makes the following inspired statement: "For whatever serum is separated into the ventricles of the brain and tissues out of them through the infundibulum to the glandula pituitaria distils not upon the palate but is poured again into the blood and mixed with it." This declaration seems to give to Richard Lower priority in regard to the hypothesis of internal secretion.

Before we proceed to the study of that part of the hormonopoietic system known as the Pituitary Body, it will be advisable to state and to define some of the special terms that will be used. This seems particularly necessary, for in the literature of the subject we find that many authors are not clear or precise in regard to the terms they employ. For instance, Fischer is very confusing in his use of the word 'hypophysis'. It is sometimes difficult to discover whether by this term he is referring to the whole Pituitary Body or only to the anterior portion (*vorderlappen*).

By the term 'hypophysis' (*ὑπό-φύειν* = to grow under) that portion of the Pituitary which is derived from the buccal ectoderm will be implied, for this part of the Pituitary grows under the encephalon; consequently the word 'hypophysis', strictly speaking, refers to the epithelial portions of the Pituitary—the pars anterior and the pars intermedia—and should only be used in this connexion. Since no extract is made from the pars anterior and the pars intermedia together and alone, the term 'hypophysin', which is commonly used, has no meaning.

By the terms 'pars anterior' and 'anterior lobe' is meant that part of the Pituitary which lies anteriorly in the human subject, and is separated from the rest of the organ by the cleft. This portion of the Pituitary, which is epithelial in structure, has been called by comparative histologists the 'distal epithelial portion', because the position of it in relation to the rest of the Pituitary varies in different animals, so much so that it may be situated inferiorly, and even posteriorly.

The 'pars intermedia' is formed by the epithelial investment of the pars nervosa and of the neck, or stalk, of the Pituitary. By comparative histologists this portion of the Pituitary has been described as the 'juxtaneural epithelium'.

The 'pars nervosa' is that part of the Pituitary which is derived from the nervous system (infundibular, or neural, process).

The pars nervosa and pars intermedia together constitute in the human subject the 'posterior lobe', or 'pars posterior'. This division into the anterior and posterior lobes arose no doubt from the ease with which they can be separated the one from the other on coarse dissection.

By the term 'infundibulin' is denoted the extract made from the posterior lobe.

PART I

THE MORPHOLOGY
OF
THE PITUITARY

PART I

THE MORPHOLOGY OF THE PITUITARY

§ i. DEVELOPMENT OF THE PITUITARY

THE scientific study of the pituitary may be said to date from the year 1838, when Rathke[1] first described the mode of origin of the hypophysis from the primitive alimentary tract. He considered, however, that the pouch described by him was entodermic in origin. Since that time numerous workers have confirmed, modified, and extended his observations; and our present settled knowledge of the development of the pituitary has been due—apart from the work of Rathke—chiefly to the labours of Balfour[2], Mihalkovics[3], Götte[4], Kupffer[5], and Herring[6]. Many other investigators have studied this question, and diverse views have been held as to the origin of the epithelial portion of the pituitary: whether it be entirely derived from the buccal ectoderm, or from the entoderm of the foregut in whole or in part; or even whether it may not arise to some extent from the wall of the cerebral vesicle. Still, it is generally believed that the two distinct parts of the pituitary—the neural and the epithelial—almost certainly arise from different sources, although ultimately they come into very intimate relationship.

The earliest stage at which the development of the human pituitary can be recognized is in the fœtus about 2·5 mm. in length, when the hypophysis is represented by what is known as the hypophysial angle (fig. 1). This angle is produced by the

[1] Rathke, H., *Arch. f. Anat. Physiol. u. Wissensch. Med.*, 1838, v, 482.

[2] Balfour, F. M., *Quart. Journ. Micr. Sci.*, 1874, xiv, 362.

[3] Mihalkovics, V. von, *Arch. f. Mikr. Anat.*, 1875, xi, 389.

[4] Götte, A., *Entwickelungsgesch. der Unke*, Leipz., 1875. Abstract: *Jahr. d. Anat. u. Physiol.*, Leipz., 1878, v, 541.

[5] Kupffer, C. von, *Sitz. d. Gesellsch. f. Morphol. u. Physiol.*, 1894, Munchen (1895), 59.

[6] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 161.

junction of the upper limit of the pharangeal membrane with the roof of the primitive stomodeum. When this membrane breaks down the hypophysial angle, which is, as was first shown by Balfour[1], ectodermal in origin, becomes deepened to form Rathke's pouch (figs. 2 and 3). Miller[2], however, who has recently investigated the development of the pituitary in the pig, believes that the ectodermal portion of the pituitary is formed from the 'brain-wall' as well as from the buccal cavity—at any rate in the species examined.

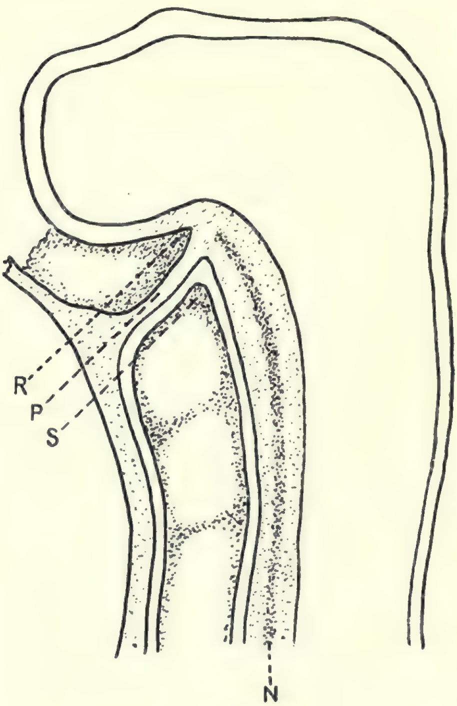

FIG 1.

Diagram to show earliest stage in the development of the pituitary. R, hypophysial angle; P, pharangeal membrane; S, Seessel's pouch; N, notocord. (*After Mihalkovics and Herring.*)

Behind the upper portion of the disappearing pharangeal membrane another angle, or pouch, is produced at the highest limit of the foregut. This is known as the pouch of Seessel[3] (figs. 1 and 2), and it is entodermal in origin. Saint-Remy[4] and Kupffer[5] thought that there is some connexion between Rathke's and Seessel's pouches in the early stages of development, but that in the adult pituitary of mammals only a rudiment of the entodermal vesicle remains.

Dursy[6] believed that the anterior lobe is entirely derived from the foregut, as did Valenti[7], who described the anterior

[1] Balfour, F. M., *Quart Journ. Micr. Sci.*, 1874, xiv, 362.
[2] Miller, W. W., *Anat. Record* (*Proc. Amer. Assoc. Anat.*), 1916, x, 226.
[3] Seessel, A., *Arch. Anat. u. Physiol.*, 1877, *Anat. Abth.*, 449.
[4] Saint-Remy, G., *Compt. Rend. Soc. Biol.*, 1895, ii, 423.
[5] Kupffer, C. von, *Sitz. d. Gesellsch. f. Morphol. u. Physiol.*, 1894, Munchen (1895), 59.
[6] Dursy, E., *Zur Entwickelungsgesch. d. Kopfes*, Tubingen, 1869, 76.
[7] Valenti, G., *Anat. Anz.*, 1895, x, 538.

lobe in amphibians as being developed from the entodermal tissues behind Seessel's pouch. But this suggestion has few supporters in the present day, although recently Miller[1] has come to the conclusion that the epithelial portion is derived partly from the ectoderm and partly from the entoderm.

The view of Dohrn[2] and others as to the origin of Rathke's pouch from the remains of a preoral gill-cleft has no modern adherents.

Reichert[3] and His[4] originally expressed the opinion that the notocord, which bends over the upper limit of Seessel's pouch, and comes into close relationship with Rathke's pouch (figs. 1 and 2), either takes part in the formation of the hypophysis or influences the invagination of Rathke's pouch. Eventually they gave up this view, and it is now considered certain by most authorities that at the most the notocord simply limits the backward extension of Rathke's pouch. Miller[1], nevertheless, claims to have shown that in the pig embryo the notocord not only influences the development of the hypophysis, but actually contributes to the formation of the pars anterior. This observer, therefore, is in agreement with almost every view that has been put forward in regard to the source or sources of the epithelial elements of the pituitary. It

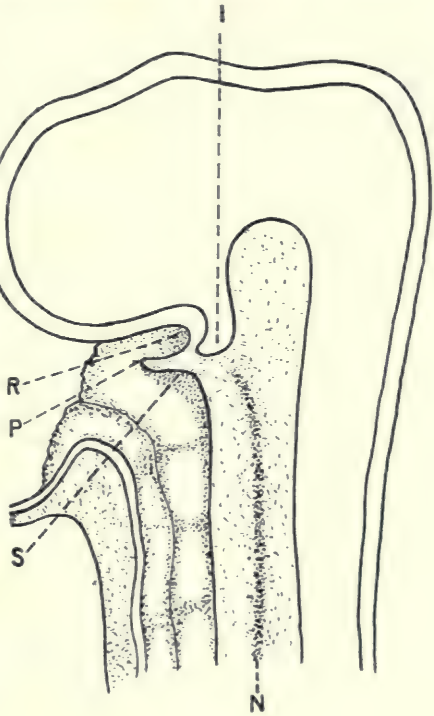

FIG. 2.

Diagram to show second stage in the development of the pituitary. I, infundibulum; R, Rathke's pouch; P, remains of pharangeal membrane; S, Seessel's pouch; N, notocord. (*After Mihalkovics and Herring.*)

[1] Miller, W. W., *Anat. Record* (*Proc. Amer. Assoc. Anat.*), 1916, x, 226.
[2] Dohrn, A. L., *Mittheilung. d. Zool. Station zu Neapel*, 1884, iii, 252.
[3] Reichert, K. B., *Das Entwickelungsleben im Wirbeltier-Reich*, Berlin, 1840, 179.
[4] His, W., *Untersuch. u. die. erste. Anlage d. Wirbeltierleibs.* Leipz., 1868, 135.

may, however, be taken as generally accepted that in most mammals the epithelial parts of the pituitary are derived only and entirely from Rathke's pouch, which is a mesial invagination from the stomodeum, and is, therefore, as already mentioned, ectodermal in origin.

The further steps in the development of the pituitary are more easily followed, owing to the clearer definition of the structures found in the larger embryos.

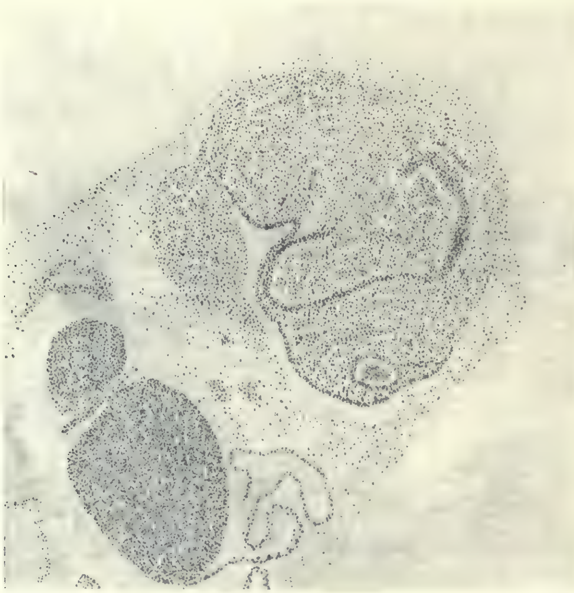

Fig. 3.

Section of the head-end of a fœtus 4 mm. in length, showing Rathke's pouch. (*From a section kindly lent by J. E. Frazer.*)

× 60.

In the earliest stages, which have already been described, there is no connective tissue between the cerebral vesicle and the buccal epithelium; consequently a very close union is formed between these two parts, and the juxtaposition of the structures concerned is maintained during the subsequent stages in the development of the pituitary (figs. 4 and 5).

According to Herring[1], when the hypophysial angle becomes

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 161.

deepened into a definite pouch by the bending forwards of the stump of the pharangeal membrane, which causes the upper surface of the angle to curve backwards and downwards, a portion of the adherent cerebral vesicle is dragged down and forms a hollow process behind the pouch. This cerebral recess represents the first appearance of the infundibular, or neural, process (fig. 2). Mihalkovics[1] was probably the first to show that the neural process is derived from the diencephalon.

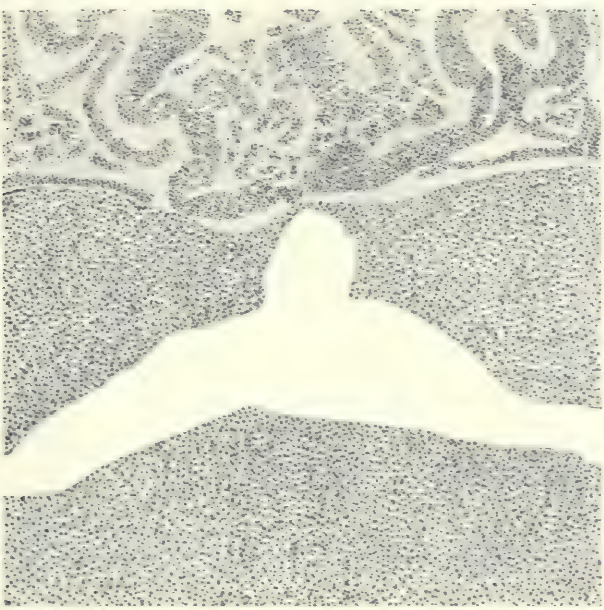

FIG. 4.

Section of the stomodeum and encephalon of a human fœtus 9 mm. in length, showing Rathke's pouch. (*From a section kindly lent by J. E. Frazer.*)

× 60.

That the same course of events is followed in all mammals is doubtful. The general contour and the relation of the epithelial portions to the neural process in the fully developed pituitary vary so much in different mammals that more work is required in regard to comparative embryology before Herring's description—accurate so far as it goes—of the formation of the infundibular process in the cat can be accepted as being invariable.

[1] Mihalkovics, V. von, *Arch. f. Mikr. Anat.*, 1875, xi, 389.

The next step in the development of the pituitary consists of the constriction of the neck of Rathke's pouch, which ultimately becomes completely closed by development of the sphenoid cartilage. A column of cells may remain, however, for some time, and mark the situation of the neck of the pouch (fig. 5). Not infrequently a collection of these cells persists

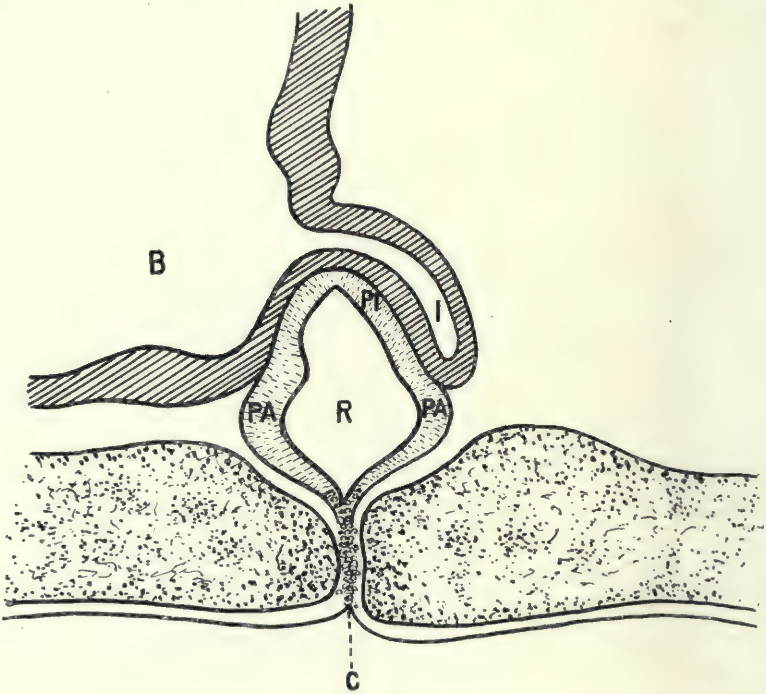

Fig. 5

Diagram to show the development of the infundibular process and the occlusion of the neck of Rathke's pouch. (*After Herring.*) B, cavity of the encephalon; C, column of cells marking the neck of Rathke's pouch; I, infundibulum; R, residual lumen of the hypophysis; PA, pars anterior, or distal epithelium; PI, pars intermedia, or juxtaneural epithelium.

throughout life and has been known to constitute the source of a neoplasm in the adult; Haberfeld[1], indeed, asserts that epithelial cells are invariably to be found so embedded, forming what he and other German writers call the *rachendachhypophyse.*

The further stages of development are well defined and may

[1] Haberfeld, W., *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1909, xlvi, 133.

conveniently be studied in the human embryo about 16 mm. in length, although the details are not quite the same in all mammals. Figures 6, 7 and 8 show different aspects from the same specimen—a 16-mm. fœtus—of the developing connexion between the hypophysis and the infundibular process of the cerebral vesicle. Most anteriorly (fig. 6) the cavity of the hypophysis is triradiate—the superior diverticulum, or process, of the cavity being, as it were, more or less independent of

Fig. 6.

Section of the pituitary region of a human fœtus 16 mm. in length, showing the infundibular process meeting the triradiate cavity of Rathke's pouch which is now shut off from the stomodeum. (*From a section kindly lent by J. E. Frazer.*) × 60.

the cerebral vesicle above. In figure 7 the infundibular process is seen to be in close relationship with the middle portion of the hypophysis: the superior diverticulum of the cavity has disappeared, and the infundibular process has become flattened out on the top of the hypophysis. Further back still (fig. 8) we find that the infundibular process has grown down past the back of the hypophysis, and that the sides, or lateral 'horns', of this structure have encircled the descending process, in the manner

described by Frazer[1]. Figure 9 represents diagrammatically composite side and back views of these relationships. Subsequently the infundibular process becomes more intimately blended with the hypophysis; and gradually in the human subject, and in most mammals, the central cavity disappears except, perhaps, for a small pouch of the cerebral vesicle at the neck. In the cat the central cavity persists.

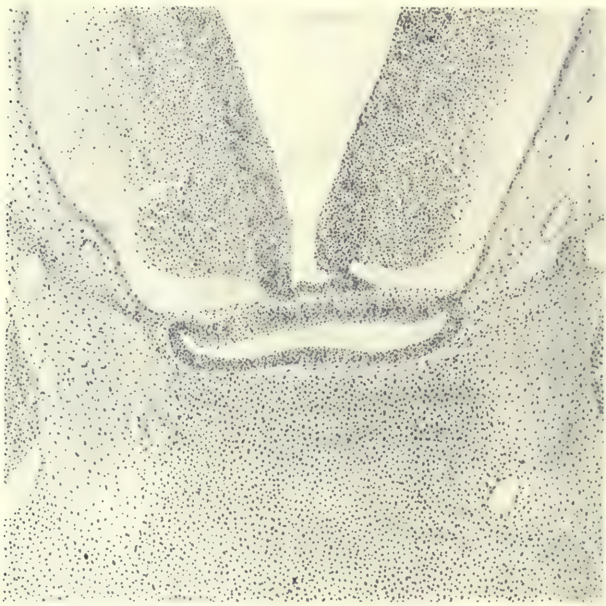

FIG. 7.

Section of the pituitary region of a human fœtus 16 mm. in length, serial to but further back than the section shown in figure 6. The infundibular process is spread out over the middle portion of the occluded pouch of Rathke. (*From a section kindly lent by J. E. Frazer.*)

× 60.

In the human fœtus 75 mm. in length the pituitary, embedded in delicate connective tissue, is found to be lying in a deep cartilaginous depression—the primitive sella turcica (fig. 10). At this stage of development all trace of the neck of Rathke's pouch has in normal circumstances disappeared, although, as already stated, a collection of cells may be enclosed in the sphenoid.

[1] Frazer, J. E., *Lancet*, 1912, ii, 875.

There are several points of interest to be noted in regard to the final stages in the formation of the pituitary. We find that the hypophysis, which originally formed a simple sac and later a triradiate cavity, increases in size by means of diverticula branching out anteriorly and laterally from the residual lumen. In this way the hypophysis becomes a much enlarged racemose body. In cross-section, therefore, at this period the hypophysis

FIG. 8.

Section of the pituitary region of a human fœtus 16 mm. in length, serial to but further back than the section shown in figure 7. The infundibular process has descended between the lateral 'horns' of the isolated Rathke's pouch. (*From a section kindly lent by J. E. Frazer.*)

× 60.

is seen (fig. 10) to be closely related to a solid neural process. The main part of the hypophysis—that is, the distal epithelial portion, or pars anterior—has a glandular appearance owing to the mode of growth already described; and the residual lumen of the hypophysis—the remains of Rathke's pouch—from which diverticula can be traced, is closely applied on its posterior surface to the neural process. This thin posterior wall of the central cavity of the hypophysis eventually forms the pars

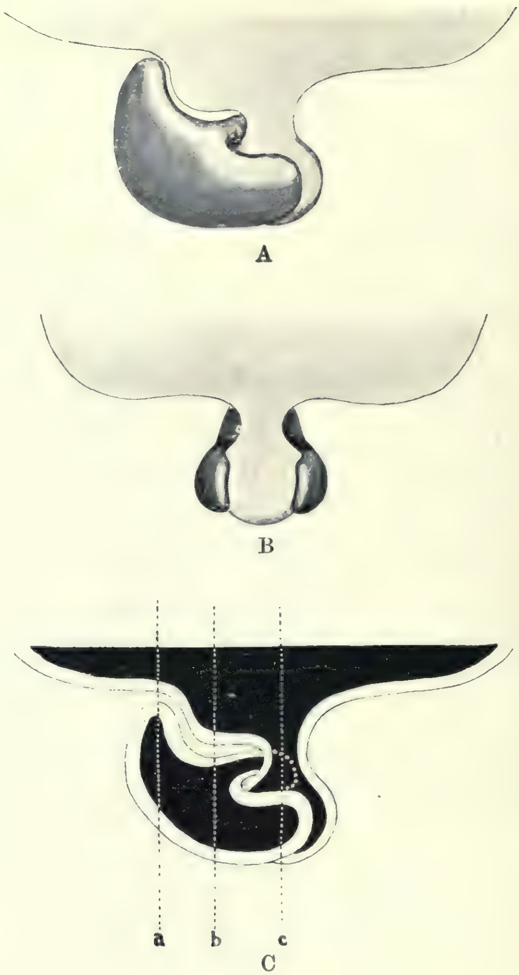

FIG. 9.

Diagrammatic representations of the pituitary of a human fœtus 16 mm. in length seen in sections in figures 6, 7, and 8.

A. Side-view.

B. Back-view.

C. Sectional side-view: *a*, line of vertical transverse section seen in figure 6; *b*, line of vertical transverse section seen in figure 7; *c*, line of vertical transverse section seen in figure 8.

intermedia, or juxtaneural epithelium (see fig. 5). It will also be observed in the section (fig. 10) that the lateral 'horns' of the hypophysis have encircled the neck of the infundibulum; and that the pars anterior extends well in front of the infundibular process (compare with figs. 6, 7, 8).

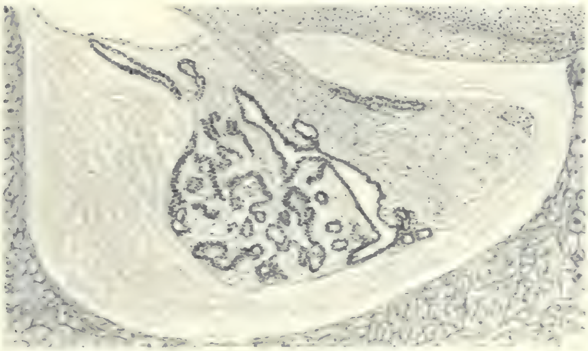

Fig. 10.

Section of the pituitary of a human fœtus 75 mm. in length. × 60.

Ultimately in mammals the branching processes of the pars anterior fuse, or become compressed together, to produce a more or less compact structure. In elasmobranchs this tubular, or branching, arrangement is the final state of development.

The last stages in the formation of the pituitary in mammals are unimportant developmentally. As we shall see, certain variations of configuration occur in the different orders; consequently the fully developed organ can best be described from anatomical—general and comparative—points of view.

§ ii. ANATOMY OF THE PITUITARY

MACROSCOPICAL ANATOMY

THE actual conformation of the pituitary and of the bony bed in which it is situated varies considerably in different animals, but in all there is a close relationship between the two so far as their outlines are concerned.

General characteristics.—If the fresh pituitary be cut in transverse section the anterior lobe is found to be soft but tough in consistence, and pink or yellowish-pink in colour, in marked contrast with the posterior lobe which is very soft and paste-like, and pearly white in colour.

In all mammals the pars anterior, or distal epithelial portion, is much larger than the pars posterior; but the relationship of the two parts the one to the other varies in the different orders, as we shall see later.

In the human subject, the posterior aspect of the pars anterior fits like a cap on the convex anterior surface of the pars posterior (fig. 11); the two lobes are separated by a narrow cleft, which, as already stated, represents the residual lumen of Rathke's pouch; and the pars nervosa is covered in varying degrees in front and laterally by the epithelium of the pars intermedia (juxtaneural epithelium). In man the pars nervosa is solid, the central cavity having disappeared in the process of development. The anterior and posterior lobes are easily disjoined by coarse dissection.

The dimensions and weight of the pituitary.—The dimensions and weight of the pituitary vary somewhat in different individuals of the same species, and these variations are dependent on the age, and to some extent on general bodily

development. But in spite of this general relationship between the size of the body and the size of the pituitary, the interesting and important fact has been noted that the pituitary is relatively larger in adult, parous females, especially in multiparæ, than in nulliparæ and in males.

In regard to the *weight* of the pituitary, Caselli[1] found that in fifty men the average weight of the pituitary was 0·667

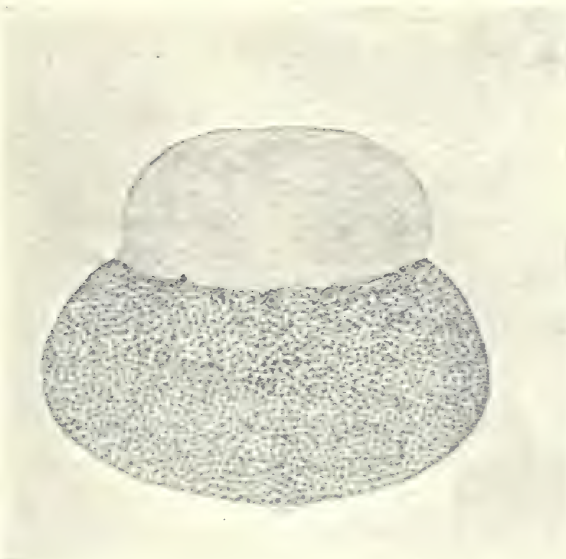

FIG. 11.

Median horizontal section of the adult human pituitary. The pars anterior is below, and the pars nervosa above.

× 5.

gramme, and in fifty women 0·731 gramme. The material for this investigation was obtained from asylums.

Halliburton, Candler, and Sykes[2] found that in eighteen adult males, the average weight of the fresh pituitary was 0·469 gramme, yet in only four cases did the organ weigh more than 0·5 gramme. On the other hand, in twenty-four females the

[1] Caselli, A., *Studi Anat. e Speriment. Fisiopatologia d. Glandola Pituitaria.* Reggio nell' Emilia, 1900.

[2] Halliburton, W. D., J. P. Candler, and A. W. Sykes. *Quart. Journ. Exper. Physiol.*, 1909, ii, 229.

average weight of the fresh gland was 0·567 gramme, and in only four of these cases did the organ weigh less than 0·5 gramme. All the material used in this investigation, also, was obtained from asylums.

Erdheim and Stumme[1], in an extensive study of this question, obtained the following results with regard to the gravimetrical differences in human pituitaries.

In males during the second decade of life the average weight was found to be 0·563 gramme; during the third decade, 0·593 gramme; and during the fourth decade, 0·643 gramme. In the later years of life the weight of the pituitary was observed gradually to decrease. With regard to females, these observers found that in nulliparæ the average weight of the pituitary was approximately the same as in men; and the maximum weight obtained during the reproductive period was 0·75 gramme. In primiparæ recently confined the average weight was 0·847 gramme; whilst in multiparæ at the end of pregnancy the average weight was 1·06 gramme. The maximum weight found in a primiparous woman was 1·10 gramme, and in a multiparous woman 1·65 gramme.

Livon[2], also, has summarized his own investigations and those of previous observers concerning the weights and sizes of the pituitary in Man and in the commoner mammals. Here we are only concerned with these questions in reference to the human subject, for it is usual for scientific investigators to make their own control observations concerning such matters in connexion with their experimental studies.

Livon's observations were made on pathological material; consequently, as he himself points out, they are, possibly, not of much value. This objection, however, obtains in practically all the investigations that have been made on this subject. Further, in the collected statistics given by this author no mention is made of sex-distinctions; and this omission renders the figures quite valueless in the light of modern knowledge.

Schönemann[3], Comte[4], and others have noted that the weight of the pituitary in Man varies according to the age; and

[1] Erdheim, J., and E. Stumme, *Beitr. z. Pathol. Anat. u. z. Allg. Pathol,* 1909 xlvi, 1.

[2] Livon, Ch., *Marseille Médical,* 1909 (No. 22), 683.

[3] Schönemann, A., *Virchow's Arch. f. Pathol. Anat. u. Physiol.,* 1892, cxxix, 310.

[4] Comte, L., *Beitr. z. Pathol. Anat. u. z. Allg. Pathol.,* 1898, xxiii, 90.

the approximate figures derived from these studies are as follows :—

New-born infant	.. .. ..	gr. 0·13
From 1 to 10 years	.. .. ..	,, 0·30
From 10 to 20 ,,	.. .. ..	,, 0·53
From 20 to 30 ,,	.. .. ..	,, 0·60
From 30 to 40 ,,	.. .. ..	,, 0·67

But in regard to these estimations, also, no allowance appears to have been made for sex-differences, so the figures are of value only in that they show the relative increases of weight with age up to a certain period. After middle life most investigators agree that there is a gradual decline in the average weight of the pituitary.

It will be seen that there is some discrepancy between the various sets of figures recorded above, even when sex was taken into consideration; but it is possible to account for this by assuming that the different observers employed different methods for collecting their material. The outstanding fact, however, is the influence of pregnancy in causing an increase in the weight of the organ. We shall have to consider this matter again when studying the histology of the pituitary in relation to its functions.

The *dimensions*, like the weight, of the normal human pituitary appear to vary somewhat. Livon[1] gives the following table of measurements, which was compiled from various sources :—

Anteroposterior diameter. mm.	Vertical diameter. mm.	Transverse diameter. mm.	Authors.
6–8	6–8	12	Sappey
8	6	12–15	Testut
5–7	5–7	15	Poirier
6–8	6	12–15	Thaon
8	6	12–15	Paulesco
10	5·5	15	Livon

Here, again, we find some divergence in the figures, and this is no doubt due to an uneven admixture of the sexes and pathological conditions present, and possibly to the employment of different methods of measurement.

Erdheim and Stumme[2], also, record their observations on

[1] Livon, Ch., *Marseille Médical*, 1909 (No. 22), 683.

[2] Erdheim, J., and E. Stumme, *Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1909, xlvi, 1.

this point. These investigators give the following average figures for adult men: transverse diameter, 14·4 mm.; anteroposterior diameter, 11·5 mm.[1]; and vertical diameter, 5·5 mm. In nulliparous adult women the average measurements were found to be 14·4 mm., 11·5 mm., and 5·9 mm. respectively.

These figures show that the dimensions, like the weights, are almost identical in adult men and nulliparous adult women; but they differ considerably from some of the collected figures given by Livon.

The sella turcica and the anatomical relations of the pituitary.—The fully developed pituitary is an intracranial organ, the epithelial part derived from the ectoderm of the stomodeum having become completely shut off at a very early period from the buccal cavity by the development of the cartilage in which the basisphenoid bone is laid down. In this way the pituitary comes to lie on the body of the sphenoid in a recess known as the 'sella turcica' (Turk's saddle) owing to its shape: the cavity is hollowed out in the centre from before backwards, and, in the human subject, slopes away at the sides, while the saddle-like appearance is further emphasized by the anterior and posterior clinoid processes which overhang the seat of the 'saddle' before and behind (fig. 12).

It is obvious that the size of the pituitary is definitely related to the dimensions of the sella turcica, but very few accurate observations have been made on the capacity of this fossa.

Gibson[2], in an examination of 107 skulls, found that there are normally very considerable variations in the size, shape, and bony relations of the sella turcica. The average dimensions of this fossa—that is, of one reconstructed from all the fossæ examined—were found to be 12 mm. in the anteroposterior diameter, and 6 mm. in the vertical.

Cope[3] examined fifty skulls and obtained the following average figures in regard to the size of the sella turcica: the anteroposterior diameter measured 10·94 mm., the transverse diameter 11·02 mm., and the vertical diameter 5·82 mm.

[1] In the original paper there is a misprint or miscalculation in the average figure, which is stated to be 21·5 mm. This error has been copied by Biedl.

[2] Gibson, W. S., *Surg. Gynæcol. Obstet.*, 1912, xv, 199.

[3] Cope, V. Z., *Brit. Journ. Surg.*, 1916, iv, 107.

According to Cushing[1], the average measurement of the sella turcica as seen in a skiagram—obviously an imperfect method —are as follows: the anteroposterior diameter is about 15 mm., and the depth of the fossa about 9 mm. These measurements

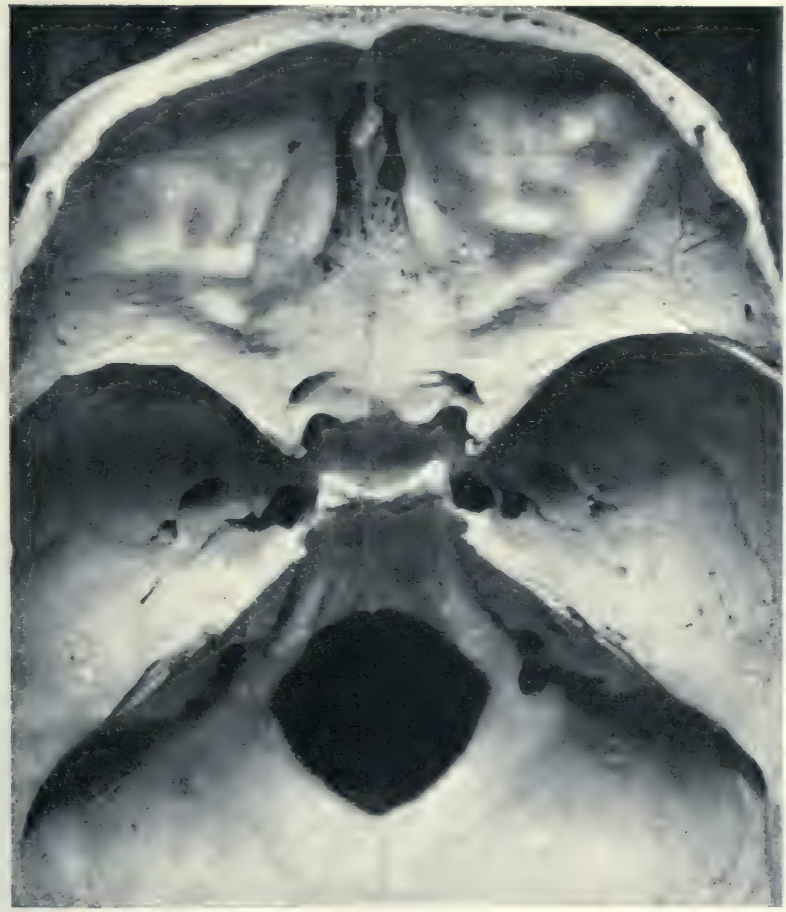

FIG. 12.

The base of the skull in the human subject with a normal sella turcica.
(*Photograph.*) $\times \frac{1}{1}$.

appear to err on the generous side, for a majority of X-ray photographs show that the sella turcica is of a smaller size (fig. 13A), although the larger may be normal (fig. 13B). X-ray

[1] Cushing, H.. *The Pituitary Body and its Disorders*, 1912.

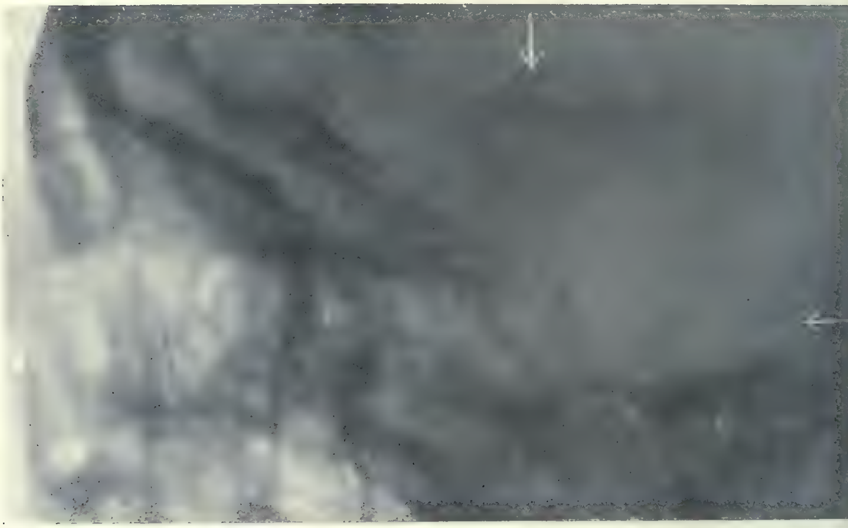

FIG. 13A.

Radiograph of a normal sella turcica in the living human subject. The antero-posterior diameter measures 11 mm. (*By Thurstan Holland.*)

× 1/1.

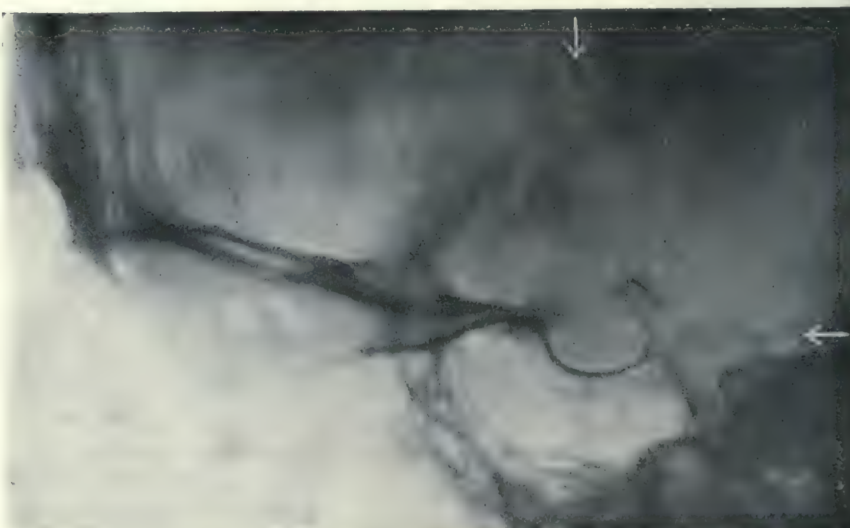

FIG. 13B

Radiograph of a normal sella turcica in the living human subject. The antero-posterior diameter measures 14·5 mm. (*This excellent photograph was taken recently by Thurstan Holland with a new method of centering.*)

× 1/1.

photographs, therefore, demonstrate the fact that even in perfectly normal individuals there is a considerable degree of variation in the size of the sella turcica.

Fitzgerald[1] has investigated the dimensions of the sella turcica in over 100 skulls of both sexes, and after making careful measurements he found that the size, and to a less extent the shape, of the pituitary fossa is related to certain measurements at the base of the skull, and that these are uninfluenced by sex.

It was observed that if measurements be taken from the tip of the ethmoidal spine to the anterior limit of the optic groove (anterior measurement), and from the opisthion to the middle of the sella turcica (posterior measurement), the length of the pituitary fossa is found to vary directly with the posterior measurement, and inversely with the anterior; that is to say, a long anterior measurement and short posterior are associated with a short fossa, and *vice versâ*.

The following table, to which appropriate headings have been added, of the average measurements of the sella turcica in relation to the average anterior and posterior cranial measurements mentioned, taken from Fitzgerald's paper, illustrates this point, and also shows the relation of these measurements to the shape of the fossa, although the latter is subject to variations.

TABLE I

ON ANTERIOR MEASUREMENT

Anterior measurements *basis cranii.*	Related average measurements of sella turcica			
	Length.	Breadth.	Front depth.	Hind depth.
Large (23–27) mm. ..	10·5 mm.	17 mm.	8·5 mm.	7·7 mm.
Medium (20–23) mm.	11 mm.	17·5 mm.	7 mm.	6·5 mm.
Small (15–20 mm.) ..	13 mm.	16·5 mm.	8 mm.	7 mm.

ON POSTERIOR MEASUREMENT

Posterior measurements *basis cranii.*	Related average measurements of sella turcica.			
	Length.	Breadth.	Front depth.	Hind depth.
Large (above 70 mm.)	14·5 mm.	17 mm.	7 mm.	7·5 mm.
Medium (65–70 mm.)	12 mm.	15 mm.	8 mm.	7 mm.
Small (under 65 mm.)	10 mm.	14 mm.	6·5 mm.	6·5 mm.

The measurements *basis cranii* are in each part of the table divided into three groups—large, medium, and small.

[1] Fitzgerald, D. P., *Journ. Anat. and Physiol.*, 1910, xliv, 231.

If we add together the average measurements of the sellæ turcicæ given in the above tables, we arrive at the following approximate average dimensions for this fossa: anteroposterior diameter, 11·8 mm.; transverse diameter, 15·1 mm., and vertical diameter, 7·2 mm.

It is difficult to explain why such divergent average figures of the measurement of the sella turcica have been obtained by different observers, unless different methods of measurement have been employed.

The relation of the sella turcica to the sphenoid bone and to the sphenoidal cells is a matter of considerable anatomical interest, and also of surgical importance as we shall see later when we consider the methods of approach to the pituitary.

In the human subject the pituitary fossa is developed in the basisphenoid (postsphenoid); but in some animals, such as the pig, and even rarely in man, the presphenoid may take part in the formation of the anterior wall of the sella turcica[1].

The craniopharyngeal canal, which becomes occluded, and so causes Rathke's pouch to be shut off from the oral cavity, passes through the anterior part of the basisphenoid, a fact that has been emphasized by Haberfeld[2], Cope[1], and others.

The sphenoidal cells are very inconstant in their configuration and their relationship to the pituitary fossa (fig. 14). In early life the sphenoidal sinuses are small, and are limited to the presphenoid[3]. During childhood they enlarge, and gradually the presphenoid becomes hollowed out. The development of the sinuses may stop at this stage, or continue until the postsphenoid is either partly or completely excavated. The sella turcica may, therefore, be situated behind, or partly above and behind, or even completely above, the sphenoidal sinuses.

There is, too, considerable variation in regard to the septa which may divide the sphenoidal cells. As a rule, the sinuses are situated mostly in the presphenoid, and are divided by a median anteroposterior septum, but this may be imperfect. If the sinuses should extend back into the postsphenoid, there is

[1] Cope, V. Z., *Brit. Journ. Surg.*, 1916, iv, 107.

[2] Haberfeld, W., *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1909, xlvi, 133.

[3] Onodi, A., *The Accessory Sinuses of the Nose in Children*, English translation, 1911.

usually a transphenoidal ridge marking the line of junction of the two parts of the sphenoid; but horizontal or vertical septa, or both, are sometimes found dividing the sinuses from side to side

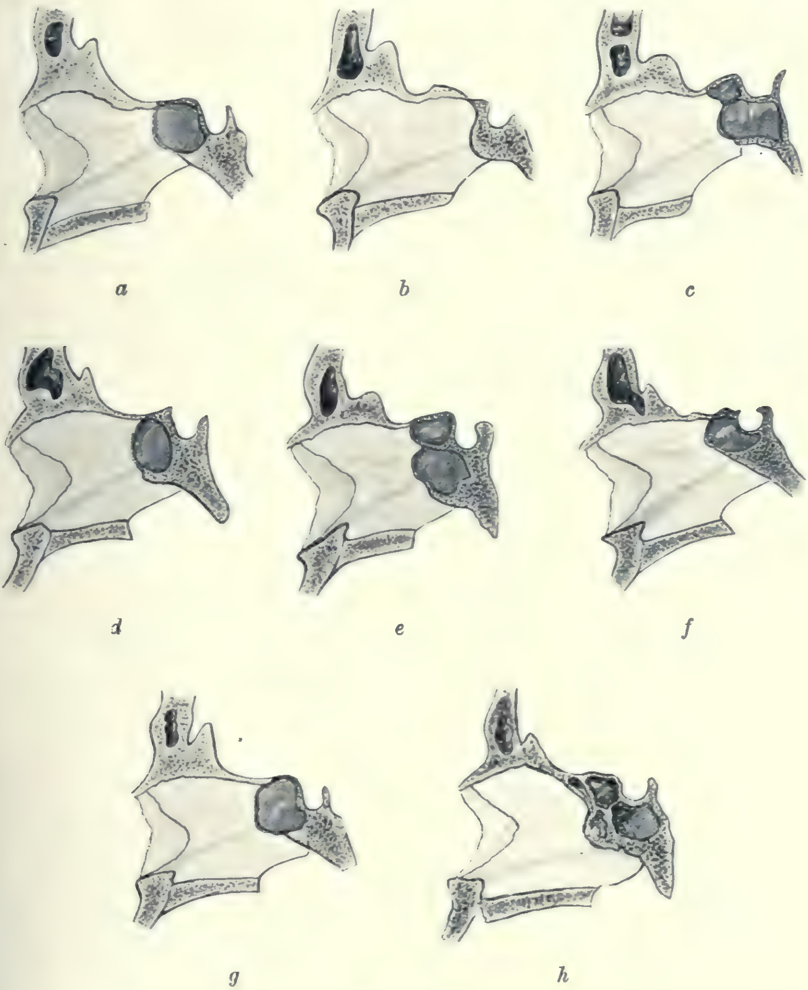

Fig. 14.

Macroscopical sections of the pituitary regions in human adults, showing variations in the conformation of the sella turcica and the related sphenoidal cells. (*After Gibson.*)

(fig. 14). These, as we shall see later, may give rise to confusion in regard to the position of the sella turcica during surgical procedures.

The cavity of the sella turcica is lined with dura mater, and it is, also, covered in by a sheet of the same membrane, which is attached to the four clinoid processes and perforated for the passage of the stalk of the posterior lobe. This infundibular stalk arises from the floor of the third ventricle at the site of the *tuber cinereum*.

Various important structures, apart from those just mentioned, are situated in immediate relationship to the pituitary. The circular sinus completely surrounds the organ. This sinus is composed of the cavernous sinuses on either side, and of the anterior and posterior communicating channels. The sella turcica itself is situated in the centre of the arterial circle of Willis, which is formed by the anterior communicating arteries joining the anterior cerebral arteries in front, by the internal carotids and posterior communicating arteries at the sides, and behind by the posterior cerebral arteries. The third nerves pass from behind forwards and above downwards on either side in close proximity to the pituitary ; and the third, fourth, ophthalmic division of the fifth, and the sixth nerves are in lateral relationship as they traverse the cavernous sinuses. Above and in front of the pituitary, and in front of the stalk, is situated the optic chiasma.

The importance of these relationships is evident when we are called upon to consider the pressure-effects which may be produced by an enlarged pituitary, or to operate upon this organ.

Vascular supply of the pituitary.—This has been studied by Herring[1] and by Dendy and Goetsch[2], and it is chiefly to these workers that we owe our knowledge of the details concerning the blood-supply of this organ.

Herring examined the internal circulation, and showed that the main vessels of the pars anterior and of the pars posterior respectively are independent of one another. He found that, if the vessels be successfully injected with carmine gelatine, the pars anterior appears to be a close network of blood-vessels (fig. 15)—previously known to be the case from histological investigations (fig. 17)—and that the arterial supply of the pars anterior is obtained from the internal carotids by means of small arteries

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.

[2] Dendy, W. E., and E. Goetsch, *Amer. Journ. Anat.*, 1911, xi, 137.

which reach their destination by passing down the stalk. Some of the veins from this part of the pituitary run up the stalk and discharge into the large cavernous sinuses—designated the 'lateral sinuses' by Herring—on either side of the pituitary; while other veins appear to pass into the pars posterior (Herring), in which they run beneath the pars intermedia (fig. 15). The posterior lobe, on the other hand, is supplied by a median artery which enters the superoposterior surface (Gentes[1]; Herring[2]). This vessel arises from the junction of two symmetrical branches from the internal carotid (Dendy and Goetsch). It may be sug-

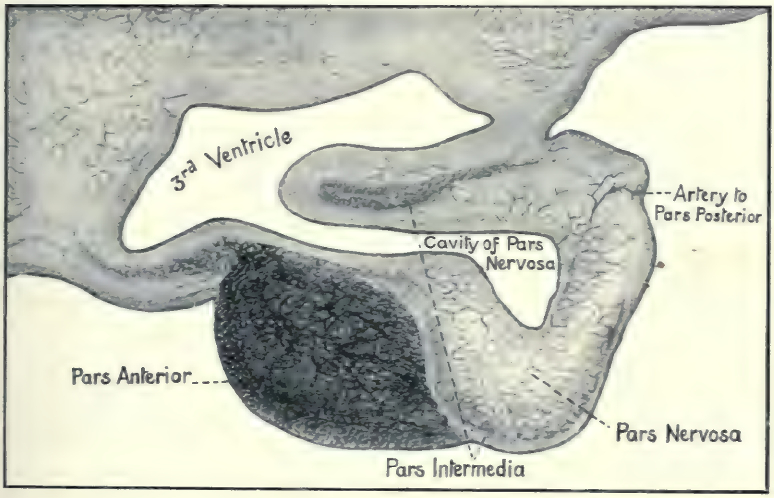

FIG. 15.

The internal circulation of the pituitary of the cat. (*After a photomicrograph by Herring of an injected pituitary.*)

gested, therefore, that this artery be called the azygos artery to the pars posterior of the pituitary.

The veins of the pars posterior are situated beneath the cells of the pars intermedia, and they unite to form venous channels, most of which pass out through the superoposterior surface in conjunction with the azygos artery, and empty into the cavernous sinuses, or into the posterior communicating channels.

It is obvious, then, that the vascular arrangement is some-

[1] Gentes, L., *Soc. Sci. d'Arcachon Trav. des. laborat*, Bordeaux, 1907, 129.

[2] Herring, P. T., *Journ. Exper. Physiol.*, 1908, i, 121.

what peculiar. In the pars anterior the small vessels are sinusoidal in arrangement and character; and, so far as the arteries are concerned, they have an origin different from that of the artery to the posterior lobe. On the other hand, there is some connexion between the veins of the two lobes. This vascular distribution is a matter of importance in regard to the physiological interdependence of the two lobes—a question which will be discussed at length later. In general terms, the internal circulation of the pituitary may be described as being distinctive in regard to the epithelial portions, whereas in the pars nervosa the distribution of the vessels is not very different from that obtaining elsewhere on the surface of the brain in the neighbourhood.

Dendy and Goetsch[1] studied especially the external connexions of the blood-vessels of the pituitary. They found that the arterial supply to the anterior lobe comes from a large number—often over twenty—small branches of the internal carotids and the anterior communicating arteries of the circle of Willis, and that these arteries converge towards the stalk; also, that many other vessels, which arise from the posterior part of the circle of Willis, pass over the corpora mamillaria to reach the posterior aspect of the stalk (fig. 16), down which run all the arteries to the pars anterior, as already described.

The venous channels from the pars anterior take a course very similar to that of the arteries (fig. 16), and pass into the circular sinus—for the most part laterally into the cavernous sinuses; while the veins from the pars posterior empty, as already mentioned, into the posterior communicating sinus or into the cavernous sinuses.

It has been stated by Dendy and Goetsch that if a parahypophysis—which is probably an accessory distal epithelial structure—be present, it has a blood-supply entirely separate from that of the rest of the pars anterior: small independent arteries reach this body from the internal carotids on either side, and, it is said, a single artery, arising in two trunks from the ununited arteries to the pars posterior of the pituitary proper, enters the posterior aspect.

This singular arterial distribution does not correspond with the view usually held that this body is an accessory pars anterior only,

[1] Dendy, W. E., and E. Goetsch, *Amer. Journ. Anat.*, 1911, xi, 137.

as is almost certainly the case. The venous blood from this structure is said to be carried away by a single small vein which enters the floor of the sella turcica. If, then, the body be an accessory organ—and almost certainly it is an accessory pars anterior, judg-

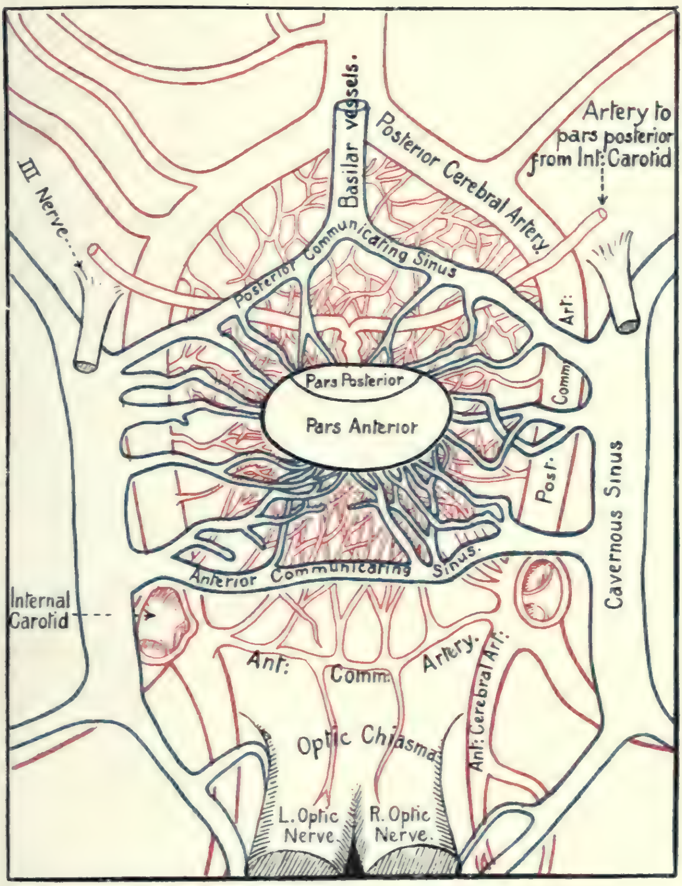

FIG. 16.

Diagram to show the external arterial and venous circulation of the pituitary seen from below, as described by Dendy and Goetsch.

ing from the structure of it and its situation over the site of the channel formed by the neck of Rathke's pouch—when it is present the separate blood-supply might permit the removal of the pituitary proper, wholly or in part, without the production of symptoms; for the blood-supply of the accessory organ being

uninjured, this structure might take on the functions of the parts removed.

Nervous connexions with the pituitary.—These are related to the sympathetic system. The evidence concerning their presence in the pituitary is histological, and will, therefore, be discussed more fully presently.

HISTOLOGICAL ANATOMY

The finer details in the anatomy of an organ, such as the pituitary, are closely related to its functional energies; consequently only a brief account of the histology of the epithelial cells will be given here. The significance of the histological appearances of the secretory elements will be discussed in connexion with the physiological aspect of the subject (p. 82). It has been mentioned that in the mammalian pituitary there are three easily recognizable parts—the distal epithelium, the juxta-neural epithelium, and the pars nervosa—and that the last two together form the pars posterior.

Pars anterior (*distal epithelium*) is composed of well-defined epithelial cells supported by a framework of fine, but tough, connective tissue, and separated into groups by large blood-vessels and sinuses whose walls are lined with a single layer of endothelium (fig. 17).

Hannover[1] in 1844 first called attention to the occurrence of more than one type of cell in the pars anterior of the frog and Man. He found that the same structure in the fowl consists almost exclusively of one variety of small cells. No further observations of importance appear to have been made until the year 1884, when Flesch[2] and Dostoiewsky[3], working independently, described cells of two different types—the chromophil and chromophobe. To Lothringer[4], however, is due the credit of showing definitely the staining affinities of these dissimilar cells.

[1] Hannover, A., *Recherches Microscopiques sur le System Nerveux*, 1844, 26.

[2] Flesch, M., *Tageblatt der 57 Versammlung Deutscher. Naturforscher und Aerzte zu Magdeburg*, 1884, 195. (Quoted by Dostoiewsky.)

[3] Dostoiewsky, A., *Arch. f. Mikr. Anat.*, 1886, xxvi, 592.

[4] Lothringer, S., *Arch. f. Mikr. Anat.*, 1886, xxviii, 257.

Many subsequent workers, among whom Rogowitsch[1], Steida[2], Pisenti and Viola[3], Schönemann[4] and Launois[5] were the most prominent, have confirmed and extended these observations.

Three varieties of epithelial cells are found in the pars anterior. Whether these cells are distinct varieties or only the same type of cell in different stages of functional activity will be discussed later. At the moment we are only concerned with the general histological appearances.

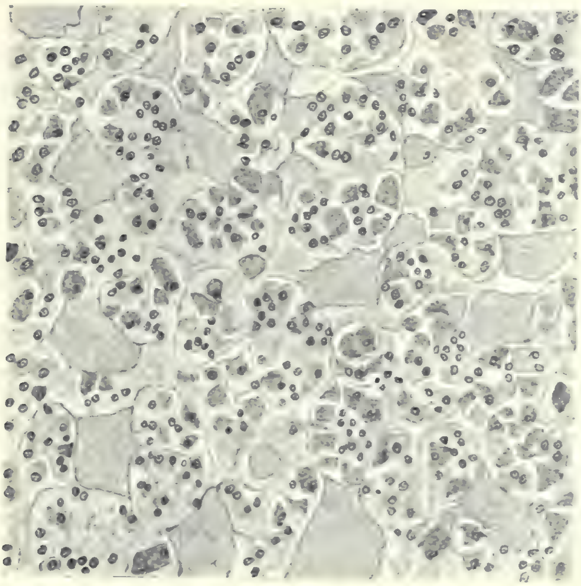

FIG. 17.

Section of the normal human pars anterior, showing large blood-sinuses. × 250.

Two of these types are chromophil in their affinity for stains, and of these, one is acidophil (eosinophil), and the other basophil (hæmatoxylinophil); and the third is neutrophil or chromophobe —that is to say, the cells stain very faintly with basic dyes. In

[1] Rogowitsch, N., *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1889, iv, 453.

[2] Stieda, H., *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1890, vii, 537.

[3] Pisenti, G., and G. Viola, *Centralbl. f. die Med. Wissensch.*, 1890, xxviii, 450.

[4] Schönemann, A., *Virchow's Archiv.*, 1892, 129, 310.

[5] Launois, P. E., *La glande hypophysaire de l'homme*, 1904.

consequence of these differences and degrees of affinity for staining agents, the normal human pituitary presents an easily recognizable appearance when examined in section under the microscope (plate 1): large brightly stained pink cells (eosinophils) are mixed —apparently indiscriminately—with big darkly stained blue cells (basophils), and small lightly stained grey-blue or faintly pink-blue cells (chromophobes).

In normal circumstances in the human subject the eosinophils, which are finely or coarsely granular, and have a centrally placed

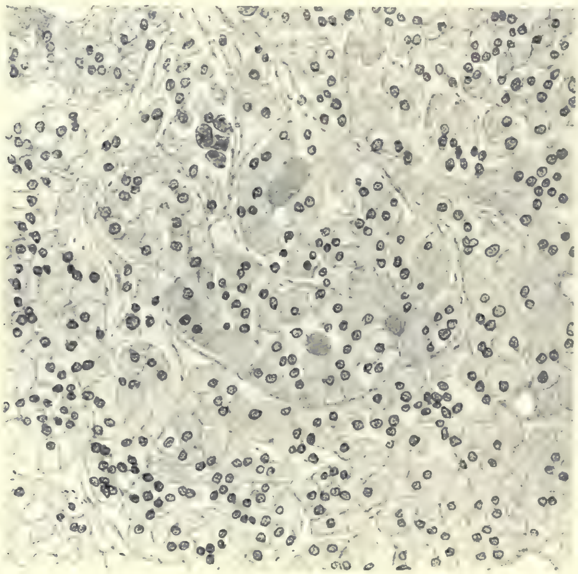

Fig. 18.

Section of the normal human pars anterior, showing acinous arrangement of eosinophil cells with granular secretion. A small group of basophils is seen in the upper part of the field.

× 250.

nucleus, predominate; but numerous basophils, both coarsely granular and homogeneous, with eccentrically placed nuclei, may be seen, especially at the periphery. Usually, chromophobe (neutrophil) cells are infrequent, although the cells of the pars anterior that abut on the cleft may tend to be chromophobe. In this situation the cells are well formed, and have definite outlines and small nuclei; but those found in the rest of the pars anterior are small and sparsely granular, and have large,

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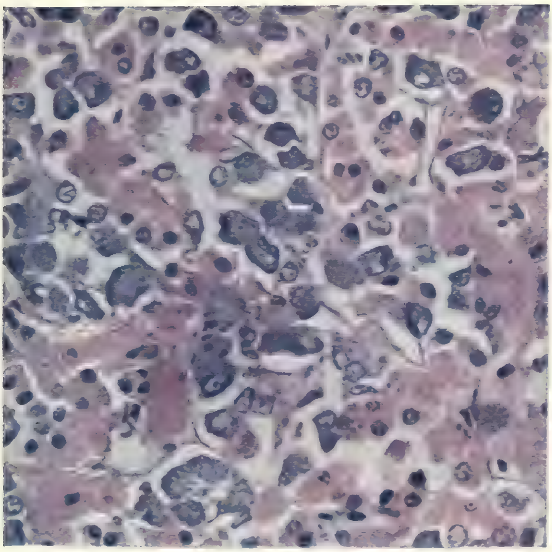

PLATE 1.

Section of the normal pars anterior in the human subject, showing basophil, eosinophil and neutrophil cells.

× 500

(Direct colour photomicrograph).

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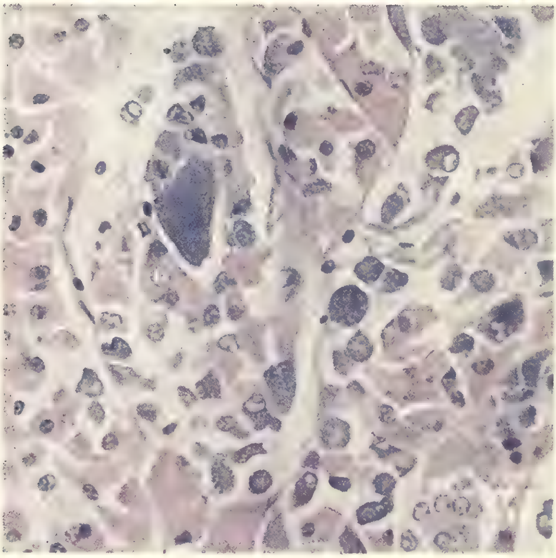

PLATE 2.

Section of the normal pars anterior in the human subject, showing a large mass of basophil colloid surrounded by neutrophil and faintly eosinophil cells.

× 500

(Direct colour photomicrograph).

clear, centrally placed nuclei with prominent chromatin fibres. As we shall see later, these appearances vary considerably in different animals, and in certain physiological and pathological states.

It is not at all uncommon to find the eosinophil cells in the pars anterior arranged in a tubular or vesicular manner, with masses of granular—not colloid—secretion in the centre (fig. 18). Occasionally, numbers of basophils are seen collected together in a somewhat similar acinous disposition (fig. 19). Nevertheless,

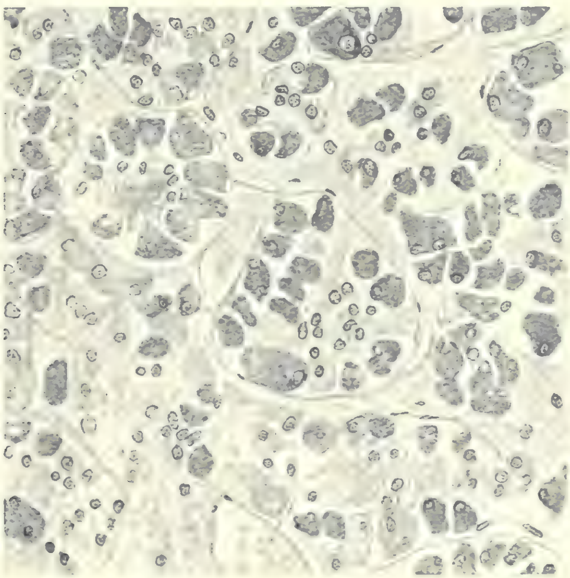

Fig. 19.

Section of the normal human pars anterior, showing groups of basophil cells. × 300.

as will be explained in discussing the physiological significance of these cells, such well-marked basophils do not surround masses of secretion, although sometimes a dark homogeneous basophil cell is seen in the wall of a vesicle surrounding basophil colloid (plate 2): for the most part the cells surrounding this substance are chromophobe or lightly eosinophil. Colloid material is, too, sometimes seen in the blood-vessels and sinuses (Thaon).

Many investigators have described nerve-fibres and cells in

the pars anterior, but Berkley[1] was the first to give a complete and accurate account of the distribution of the nervous elements. This investigator found that only *sympathetic nerve-fibres* from the carotid plexus are present, and that there are no true nerve-cells or fibres in this part of the pituitary. These sympathetic fibres, which are very fine and varicose, come off the main stem approximately at a right angle, cross the sinuses to run an irregular course among the epithelial cells, and finally break up into

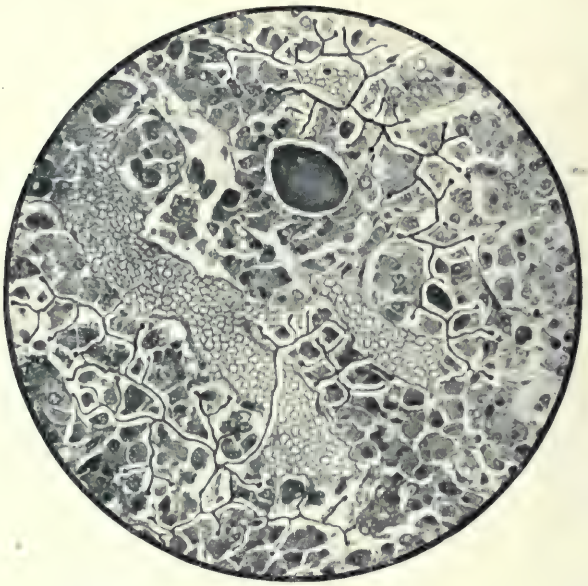

FIG. 20.

Section of the normal human pars anterior, showing sympathetic nerve fibres. (*Partly photomicrographic.*)

× 300.

branching terminations with numerous ball-shaped endings which lie in the intercellular tissue (fig. 20).

Thaon[2] states that he has investigated the matter carefully and has failed to find any *lymphatics* whatsoever in the pars anterior. Caselli[3], however, asserts that lymphatics are abundant,

[1] Berkley, H. J., *Brain*, 1894, xvii, 515.

[2] Thaon, P., *L'hypophyse*, Paris, 1907.

[3] Caselli, A., *Studi Anat. e Speriment. Fisiopatologia d. Glandola Pituitaria.* Reggio nell' Emilia, 1900.

while Pisenti and Viola[1] and Herring[2] state that there is considerable doubt as to whether they exist or not. Edinger[3] believes that lymph-spaces separate the epithelial cells from the blood-sinuses. Most observers, however, agree that lymphatics, if present, must be extremely few in number.

Pars intermedia (*juxtaneural epithelium*). This portion of the pituitary body was first identified and described by Peremeschko[4]. As we have seen, the juxtaneural epithelium is differentiated from the distal epithelium (pars anterior) in the process of development. It is for the most part applied to the surface of the pars nervosa, which abuts on the cleft, and to the region of the neck; but the extent and distribution of the juxtaneural epithelium varies enormously in different animals. In some, such as the cat and dog, the distribution is very extensive: not only is the epithelium applied to the surface of the pars nervosa, completely enclosing it, and collected in a large mass around the neck, but it extends, also, in a tongue-shaped projection along the base of the brain above the pars anterior (figs. 47 and 51). In these animals, too, the cells in the neighbourhood of the neck and above the pars anterior are arranged in the form of vesicles, which enclose much granular secretion (figs. 48 and 52). In the human pituitary colloidal secretion is sometimes found in the pars intermedia above the cleft, and also in the cleft itself. This secretion in the pars intermedia and cleft of the human pituitary is most frequently seen in the female during and just after pregnancy, and in old age in both sexes. The juxtaneural epithelium, however, in the human subject is very scanty and forms a thin layer covering the pars nervosa where it adjoins a very narrow cleft (fig. 21). At the upper limit of the cleft and around the stalk the cells are more numerous, but never occur in large numbers.

The juxtaneural epithelium is usually faintly basophil, or neutrophil, in its staining reactions. The cells are finely granular and polygonal in shape. In those animals, such as the cat, in which there are many layers of epithelium lining the cleft, the

[1] Pisenti, G., and G. Viola, *Centralbl. f. die Med. Wissensch.*, 1890, xxviii, 450.
[2] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.
[3] Edinger, L., *Archiv. f. Mikr. Anat.*, 1911, lxxviii, 496.
[4] Peremeschko (no initial in the original), *Virchow's Archiv.*, 1867, xxxviii, 329.

distribution is unequal; consequently projections of wedge-shaped epithelial masses are frequently seen dipping down into the pars nervosa. In these circumstances, also, the epithelial elements lining the cleft are often flattened on the free surface and are triangular in shape, with an angle dipping down into the cells beneath; and the cells which are in contact with the pars nervosa may, also, resemble in shape the foot-cells of the testicle. In many animals—but never in man—supporting spindle-shaped cells

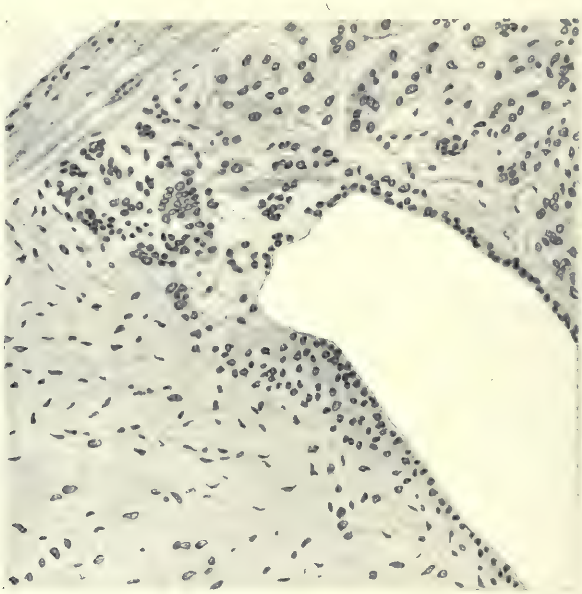

Fig. 21.

Section of the normal human pituitary, showing the pars intermedia above and abutting on the cleft.

× 250.

arranged vertically to the surface are seen among the epithelial elements, covering the pars nervosa; sometimes, as in the lemur, there is a considerable amount of connective tissue, in connexion with which there may be blood-vessels, dividing the cells into groups.

At the junction of the pars intermedia and the pars anterior there is often an almost insensible gradation from one to the other. In these circumstances the line of junction only can be identified by the difference in the staining reactions, by the

shape and size of the cells, and by the assumption of a vesicular arrangement in the pars intermedia different from that found in the pars anterior.

As we have seen, usually no blood-vessels or lymphatics are found in the juxtaneural epithelium lining the cleft, but many large blood-vessels and much supporting connective tissue are found among the vesicles above the pars anterior and around the neck in those animals in which this arrangement is well defined (fig. 49). *Lymphatics*, also, according to Herring[1], are to be found in this region. Thaon[2], on the other hand, denies the presence of lymphatic vessels.

The *nervous elements* of the pars intermedia will be discussed in connexion with the pars nervosa.

Pars nervosa is chiefly composed of neuroglial cells and fibres (fig. 22), but there is a small amount of connective tissue, and Thaon[2] has observed collagen-fibres. In some animals there is a central cavity communicating with the third ventricle, and lined with ependyma-cells ; but in man and most mammals this portion of the pituitary is solid.

In certain circumstances large cells of the pars intermedia may be found in the pars nervosa, and even large masses of neutrophil granular secretion derived from these cells or from the pars intermedia directly. The importance of these cellular and secretory incursions will be discussed later in connexion with their functional significance.

The configuration and distribution of the neuroglia-cells and their fibres have been depicted by many writers ; and Berkley[3], Osborne and Vincent[4], and other observers have described the presence of true nerve-cells and nerve-fibres in this part of the pituitary. Berkley, if I understand him correctly, also states that the epithelial cells of the pars intermedia abutting on the cleft are enclosed in a capsule of ependyma-cells which send long processes down among the epithelial elements. This observation has not been confirmed—indeed, on developmental grounds such a phenomenon is incapable of belief.

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.
[2] Thaon, P., *L'hypophyse*, Paris, 1907.
[3] Berkley, H. J., *Brain*, 1894, xvii, 515.
[4] Osborne, W. A., and S. Vincent, *Brit. Med. Journ.*, 1900, i, 502.

Many types of neuroglial cells are to be found, and these varieties relate chiefly to the profusion or otherwise of the processes arising from them.

According to Berkley the true nerve-cells are situated chiefly in the lower and anterior part of the pars nervosa. This author has divided them into two groups—those having one dendrite and those having more than one. Caselli[1], Herring[2], and most other observers deny the existence of true nerve-cells in the pars posterior. They believe that the nervous elements consist

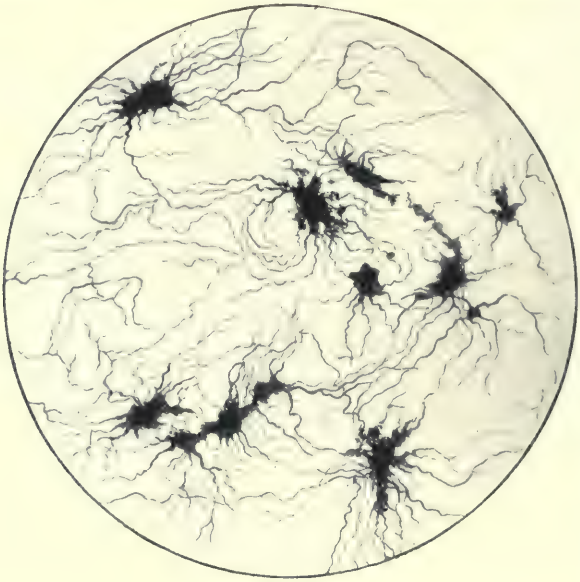

FIG. 22.

Neuroglial cells and fibres in the pars nervosa of the cat. (*After Herring.*)

entirely of neuroglial and ependymal tissues. With regard to the ependymal cells, these are found in the neighbourhood of the neck, and sometimes as inclusions in the centre of the pars nervosa in those animals in which the central cavity has been obliterated in the process of development.

No evidence has yet been adduced to show that the sympathetic nerves leave the blood-vessels in the pars nervosa as in

[1] Caselli, A., *Studi Anat. Speriment. Fisiopatologia d. Glandola Pituitaria*, Reggio nell' Emilia, 1900.

[2] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.

the case of the pars anterior. It has been suggested, however, that such fibres may possibly reach the pars intermedia from the pars anterior. The internal blood-supply of the pars posterior has already been described (p. 24).

Special attention has been directed by Kohn[1] and others to a peculiar pigment which has long been known to exist in the neuroglial fibres of the pars nervosa. Fischer[2] considers that this substance is the result of degeneration in old age.

The composition and origin of this pigment has not been discovered, but according to Biedl[3], it has been shown to be neither a fat nor a lipochrome.

Clunet and Jonnesco[4], also, have made a careful study of this material. They have found that it is possible with the naked eye to observe the pigment in unstained sections held up to the light : it is chiefly seen in the posterior part of the pars nervosa, although it may be distributed throughout. The granules are more or less spherical, and are brownish-yellow or greenish in colour.

It was found by these investigators that neither hydrochloric acid nor acetic acid has any effect on the pigment, but that sulphuric acid turns it black without dissolving it. It is insoluble in alcohol, xylol, benzene, chloroform, ether, and cedarwood oil. Strong solutions of ammonia and of caustic potash and soda will only affect this substance after prolonged contact —that is to say, after twenty-four or more hours—when it may be completely dissolved.

The pigment does not give the iron reactions. It is not turned brown by osmic acid, nor coloured red by sudan III and scharlack R ; and it is not stained by hæmatoxylin, hæmatin, or safranin, but it is changed to an intense black by iron-hæmatoxylin, and blue by Giemsa's stain. It is tinted, also, by a few of the rarer dyes.

Livon and Peyron[5] have discussed the importance of this

[1] Kohn, A., *Archiv. f. Mikr. Anat.*, 1910, lxxv, 337.

[2] Fischer, B., *Hypophysis, Akromegalie und Fettsucht*, Wiesbaden, 1910.

[3] Biedl, A., *Innere Sekretion*, 2nd ed., 1913.

[4] Clunet, J., and V. Jonnesco, *Compt. Rend. Soc., Biol.*, 1910, lxix, 626.

[5] Livon, C., and Peyron (no initial in the original), *Compt. Rend. Soc., Biol.*, 1911, lxx. 730.

substance in a somewhat vague communication. These authors look upon the pigment as a product elaborated by the neuroglial elements from the secretion of the glandular portion of the pituitary; but whether this is effected by a process of assimilation or deposition they were unable to discover.

Histological appearances of the pituitary at different periods of life.—Very few observers have published accounts of the histological appearances of the pituitary at different periods of life, although many writers have assumed that differences exist at various ages. Our own somewhat scanty observations agree with the findings of Thaon[1].

In early childhood the pars anterior appears to be inactive. The epithelial cells are small and closely packed; they show very little evidence of differential staining, and the blood-sinuses contain but little blood. The cells of the pars intermedia, also, are shrunken in appearance, and colloid is never seen in this region, but small masses of granular secretion may be found in the pars anterior.

About puberty functional development is to be observed: the epithelial cells become large, and show faintly differential staining. After this period the cells gradually come to resemble the ordinary adult types, the blood-sinuses become distended and the whole organ shows normal activity.

In old age the pituitary is very little different in appearance from the adult organ: the epithelial elements are active and stain well. It is, however, certainly more usual to see masses of colloid in the cleft and in the vesicles of the pars intermedia than is usual in middle life apart from pregnancy. But there is no evidence of senile atrophy as described by Caselli[2]; although, pathologically, sclerotic changes in the pituitary may be observed in association with similar lesions elsewhere.

Fischer[3], as already stated, describes the deposit of pigment in the neuroglial fibres as an old-age change.

Geurrini[4] examined young guinea-pigs and rabbits, and found

[1] Thaon, P., *L'hypophyse*, Paris, 1907.

[2] Caselli, A., *Studi Anat. e Speriment. Fisiopatologia d. Glandola Pituitaria*, Reggio nell' Emilia, 1900.

[3] Fischer, B., *Hypophysis, Akromegalie und Fettsucht*, Wiesbaden, 1910,

[4] Guerrini, G., *Arch. Ital. de Biol.*, 1905, xliii, 1.

that so long as they were suckled the pituitary presented an inactive appearance, but that activity became evident as soon as they were weaned. Thaon[1], however, could find no such differences between the pituitaries of lambs and older sheep.

[1] Thaon, P., *L'hypophyse*, Paris, 1907.

§ iii. COMPARATIVE ANATOMY OF THE PITUITARY

SINCE most of the histological and physiological investigations in regard to the pituitary have been carried out in connexion with the organs obtained from the lower animals, we are in possession of a considerable amount of information concerning the comparative features of this organ in the commoner mammals, such as the cat, dog and rabbit; but more primitive mammals and the lower vertebrata have not been investigated quite so completely.

Nevertheless, thanks to the researches of Andriezen[1], Haller[2], Sterzi[3], Gentes[4], Herring[5], Tilney[6], and a few others, we have some certain knowledge concerning the pituitaries of the lowest vertebrates—the commoner fishes, amphibians, reptiles and birds.

The importance of such comparative studies is very great, not only from a morphological point of view, but also from a physiological.

CYCLOSTOMATA

Petromyzontes.—Andriezen[1], so far as I can discover from his paper which is somewhat obscure and involved, claims to have shown by an investigation of *ammocœtes*—the larval stage of *petromyzon planeri*—that the primitive pituitary, which he

[1] Andriezen, W. L., *Brit. Med. Journ.*, 1894, i, 54.

[2] Haller, B., *Morphol. Jahr.*, 1896, xxv, 31.

[3] Sterzi, A. (quoted by Gentes [4]), *Atti dell'Acad. Sci. Veneto-Trentino-Istriana*, 1904, i, 72.

[4] Gentes, L., *Soc. Sci. d'Arcachon, Travaux des laborat.*, Bordeaux, 1907, 129.

[5] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i. 121; *idem*, 1908, i, 261; *idem*, 1913, vi, 73.

[6] Tilney, F., *Memoirs Wistar Instit. Anat. and Biol.*, Philadelphia, 1911 (No. 2), 1.

describes as being composed of three parts, is a water-vascular organ. There is, he says, a median subneural glandular organ arising from the buccal epithelium, a duct lined with ciliated epithelium connecting the buccal and neural cavities, and a group of nerve-cells closely investing the upper (neural) opening of the duct. From these observations he draws the following conclusions. First, the open duct implies the presence of a water-vascular system—a system whereby water is admitted from the buccal cavity to the neural canal, in order that oxygen may be conveyed to the nervous elements and waste products removed by way of the posterior aperture. Second, the glandular organ pours its secretion into the neurobuccal duct, wherein it is carried by the water-stream into the neural canal. Third, the duct and attached sensory (selective) nervous elements are only functional in very primitive vertebrates, and atrophy in the higher; and in the latter the glandular portion which persists secretes into lymphatics, and thence into the blood-stream.

Sterzi[1] and Gentes[2] have examined the fully developed *petromyzon fluviatilis*, and have given a very complete description of the pituitary in this creature.

According to Gentes, the hollow infundibular process extends downwards into the narrower *recessus hypophyseus*, the wall of which forms the *lobus infundibuli*. Below and around the convexity of this lobe is the juxtaneural epithelium. This is separated from the infundibular process by connective tissue and vessels. Gentes refers to this epithelial layer as the 'posterior lobe'; and he divides the distal epithelial portion into two lobes —an anterior and a middle (fig. 23)—which are separated from one another by connective tissue, as is the middle lobe from the 'posterior'. Sterzi first noted that the middle lobe is chromophobe in its reaction to the usual stains, while the anterior and 'posterior' lobes are chromophil. The chromophil cells appear to be of one character only and stain best with iron-hæmatoxylin. The middle lobe is approximately of the same size as the anterior.

Herring[3], also, has examined the pituitary of the lamprey,

[1] Sterzi, A. (quoted by Gentes [2]), *Atti dell' Accad. Sci. Veneto-Trentino-Istriano*, 1904, i, 72.

[2] Gentes, L., *Soc. Sci. d'Arcachon, Travaux des laborat.*, Bordeaux, 1907, 129.

[3] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1913, vi, 73.

and his description agrees in all essentials with that given by Gentes.

Tilney[1] states that the pituitary in this vertebrate is recognizably representative of that found in the higher vertebrates, although he noted certain peculiar features. There is, he states, a definite pars anterior (distal epithelial portion), but the cells are arranged in parallel columns set perpendicularly to the base of the brain. These cells stain indifferently with hæmatoxylin.

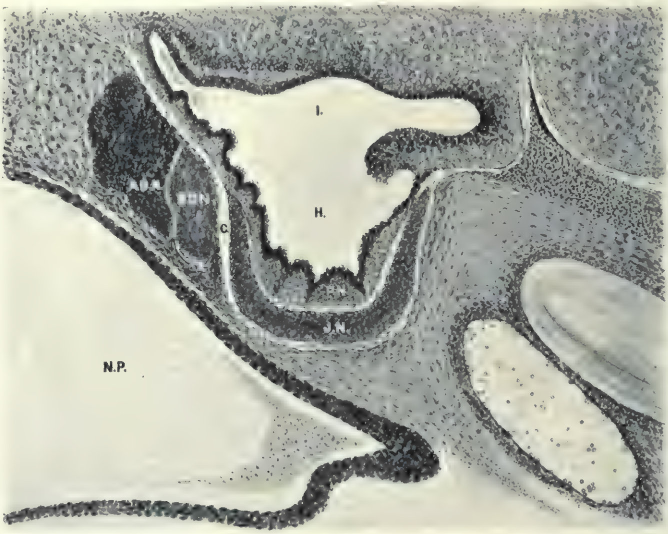

FIG. 23.

← Anterior direction.

Median sagittal section of the pituitary of the lamprey (*petromyzon fluviatilis*). (*After Gentes.*) I, infundibular process (3rd ventricle); H, infundibular recess; PN, pars nervosa; JN, juxtaneural epithelium; ADN, chromophil portion of distal epithelium; BDN, chromophobe portion of distal epithelium; C, cavity; NP, nasopharangeal canal.

The cells of pars intermedia (juxtaneural epithelium) are arranged in convoluted cords, they stain deeply with hæmatoxylin, and are attached to a short but distinct infundibular process. Tilney could find no evidence of a residual cleft, nor did he discover colloid material or supporting connective tissue among the epthelial cells.

[1] Tilney, F., *Memoirs Wistar Instit. Anat. & Biol.*, Philadelphia, 1911 (No. 2), 1.

PISCES

Elasmobranchii.—According to both Gentes[1] and Herring[2], in these primitive fishes the pituitary is represented practically entirely by an organ of a glandular character (distal epithelium).

Gentes[1] states that there is no posterior lobe in elasmobranchs; but Herring found that in the skate there is a "thin lamina of nervous tissue which bounds the infundibular cavity and passes into the tissue of the pituitary", but that this is the "nearest approach to anything resembling a posterior lobe". It may be assumed, therefore, that, even if the pars nervosa be present in the restricted sense described by Herring, it is prob-

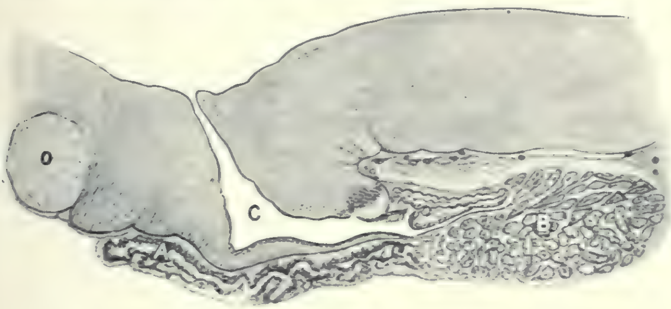

FIG. 24

← Anterior direction.

Median sagittal section of the pituitary of the skate (*raia batis*). (*After Herring.*) A, distal epithelium enclosing cavity; B, main part of distal epithelium; C, infundibular cavity; O, optic chiasma.

ably quite functionless in these creatures; indeed, Herring[2] has shown that no physiologically active pressor extract can be made from the pituitary of elasmobranchs, although such a product is easily obtainable from the pituitaries of the higher vertebrates.

In the *skate* (*raia batis*) the pituitary forms an elongated body: the anterior portion extends forwards like a tongue, while posteriorly the organ is oval in shape (fig. 24). In the centre of the anterior prolongation of the glandular tissue there is a ventricle, or canal; and the hollow infundibular process is in close proximity to the upper surface of this glandular structure.

[1] Gentes, L., *Soc. Sci. d'Arcachon, Travaux des laborat.*, Bordeaux, 1907, 129.

[2] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, vol. i, p. 261; *idem*, 1913, vi, 73.

On histological examination the organ is found to be made up of what at first sight appear to be acini—closely resembling, indeed, the acini seen in the fœtal pituitary of the higher mammals (see fig. 10, p. 13); but, as Gentes has pointed out in the case of *torpedo marmorata*, the central lumina are blood-channels ('*capillaire sanguin sinusoidal*') surrounded by glandular cells (fig. 25). This observation, which has been confirmed by Herring, is of considerable importance, for it

FIG. 25.

Section of the distal epithelial portion of the pituitary of the skate (*raia batis*), showing the glandular arrangement of columnar cells around blood-channels lined with endothelium. (*After Herring.*)

demonstrates clearly that in the primitive state the pituitary, which consists only of a glandular structure surrounding sinuses, secretes directly into the blood-stream. In the elasmobranchs there is no differentiation in the staining reactions of the secretory cells. According to Herring, no chromophil elements are to be seen. The cells are columnar in shape with basal nuclei and clear free surfaces—in fact, typical secreting cells.

Tilney[1] states that in the *dog-fish* (*squalus acanthias*) the infundibular process is well developed, but is situated anteriorly.

Before continuing further the study of the comparative anatomy of the pituitary reference must be made to a peculiar structure found in relation to the pituitary, which is more or less well developed in nearly all vertebrates below the mammals, and is known as the '*saccus vasculosus*'.

This structure is very prominent in elasmobranchs and in many teleosts, although according to Gentes[2] it is rudimentary or absent in some of the higher fishes. Herring[3] states that the saccus vasculosus is bilobed and bilateral in the skate (*elasmobranch*), and single and central in the cod (*teleost*).

The structure of the saccus vasculosus is simple: it consists of a thin-walled sac or sacs, lined with columnar epithelium and supplied by numerous blood-vessels. The saccus vasculosus opens by a wide orifice, or by several orifices, into the cavity of the infundibular process; consequently Gentes[2] believes that it is analogous to the choroid plexus, and that it secretes cerebrospinal fluid.

The saccus vasculosus, from its intimate relationship to the pituitary, may in the lower vertebrates give rise to difficulty in the interpretation of the histological appearances of that organ unless the propinquity of the two structures be fully recognized. In the skate the saccus vasculosus is bilobed and bilateral in position; consequently it is not seen in mesial sections.

Teleostei.—In the bony fishes definite differentiation of the various parts of the pituitary is seen, but in the diverse species the relation of these parts to one another varies.

In the *cod* (*gadus morrhua*), which is described by Herring[4], the chromophil cells, which may be considered representative of the pars anterior proper of mammals, are found in a compact mass sandwiched between neutrophil cells (fig. 26). The two groups of neutrophil cells are in close relationship with nervous

[1] Tilney, F., *Memoirs Wistar Instit. Anat. and Biol.*, Philadelphia, 1911 (No. 2), 1.

[2] Gentes, L., *Soc. Sci. d'Arcachon, Travaux des laborat.*, Bordeaux, 1907, 129.

[3] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 211; *idem*, 1913, vi, 73.

[4] Herring, P. T. *Quart. Journ. Exper. Physiol.*, 1908, i, 261; *idem*, 1913, vi, 73.

processes. There is no doubt that these neutrophil cells represent the pars intermedia of mammals, for they are found invading the nervous outgrowths which are composed of neuroglial and ependymal cells and fibres. The pars nervosa proper, then, is a branching structure, and is, therefore, deeply indented by collections of the chromophobe cells. In the centre of the main body of the pars nervosa lies the cavity of the infundibulum, which is directly connected with the third ventricle of the brain.

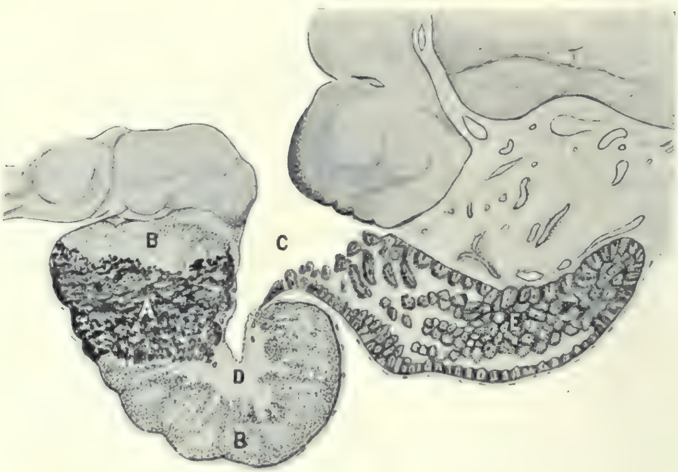

FIG. 26.

← Anterior direction.

Median sagittal section of the pituitary of the cod (*gadus morrhua*). (*After Herring.*) A, distal epithelium; B, juxtaneural epithelium; C, cavity of infundibular process; D, pars nervosa; E, saccus vasculosus.

Behind the pituitary of the cod and in the mid-line lies the saccus vasculosus, the interior of which is also in direct communication with the ventricle.

In the *common eel* (*anguilla vulgaris*), which has been investigated by Tilney[1], we reach an interesting stage in the evolution of the pituitary (fig. 27). According to this investigator, the pars anterior is well defined in a central and two lateral masses, while the pars posterior is almost equal in size to the pars anterior. There is no cleft between the two parts. The cells

[1] Tilney, F., *Memoirs Wistar Instit. Anat. and Biol.*, Philadelphia, 1911 (No. 2), 1.

in the central mass of the pars anterior are arranged in definite acini, and in staining reaction are strongly basophil; on the other hand, those in the lateral portions are acidophil, and are arranged in columns with intervening blood-spaces. The pars posterior shows a hollow infundibular process which forms aborizations backwards and downwards, giving rise in these directions to primary, secondary and tertiary diverticula all of which are hollow and are lined with ependyma-cells. The spaces between these branches are filled with lightly staining basophil epithelial cells; in other words, the hollow infundibular projections bury

Fig. 27.

← Anterior direction.

Median sagittal section of the pituitary of the eel (*anguilla vulgaris*). (*After Tilney.*) PA, distal epithelium; PI, juxtaneural epithelium; C, infundibular cavity; PL, lateral masses.

themselves in a mass of pars intermedia (juxtaneural) epithelium. This arrangement gives the pars posterior the appearance of an actively secreting gland the cells of which surround lumina leading to the ventricle of the brain; and there can be no doubt that it is partly this interesting disposition—which is also described by Gentes—that has led to belief that the pressor substance produced in the pars posterior is conveyed to the cerebrospinal fluid in the third ventricle. Herring[1] has supported this view, which he originated, by other evidence that will be discussed in the appropriate place.

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.

AMPHIBIA

The commoner species of amphibian animals have been investigated by several observers: Haller[1], Sterzi[2], Gentes[3] and Herring[4], especially, have contributed valuable information concerning these creatures.

Ecaudata.—Gentes investigated two genera of ecaudata (*bufo vulgaris* and *rana esculenta*), and found that there were no essential differences between them in regard to the pituitary. Tilney examined *rana sylvatica.* The descriptions of Gentes, Tilney and Herring are more or less in agreement, in regard to the main particulars, with those of the earlier observers; consequently the pituitaries of this order of amphibians must closely resemble each other.

The organ is triangular in shape and the pars nervosa and juxtaneural epithelium are situated above and in front of the distal epithelium. Tilney could find no residual lumen in the adult animal, but Gentes represents this cavity to be of considerable size. The last-named observer points out, also, that there is a number of large vessels in the pars nervosa, a phenomenon which may be of physiological importance.

There is a considerable difference between the amphibian pituitary and that seen in the bony fishes and reptiles. In the animals under discussion the posterior lobe is relatively small; indeed, in some cases it is little more than the adjacent wall of the hollow infundibular process—the 'hypophyseal recess' of Gentes being entirely absent.

The juxtaneural epithelium is closely attached to this imperfect infundibular lobe which may slightly indent the epithelial layer, but there is no hollow branching as in teleosts. The cells of the juxtaneural epithelium are closely packed and are chromophobe in their staining affinities.

The pars anterior is entirely eosinophil in its tinctorial affinity (Tilney), and according to Gentes there is no connective tissue

[1] Haller, B., *Morphol. Jahr.*, 1896, xxv, 31.

[2] Sterzi, A. (quoted by Gentes [3]), *Atti dell' Accad. Sci. Veneto-Trentino-Istriana*, 1904, i, 72.

[3] Gentes, L., *Soc. Sci. d'Arcachon, Travaux de laborat.*, Bordeaux, 1907, 129.

[4] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1913. vi, 73.

between the cells, but a very extensive vascular sinusoidal arrangement of the vessels. Attached on either side to the central part of the pars anterior are two lateral masses, called by Gaupp[1] the lateral lobes of the hypophysis.

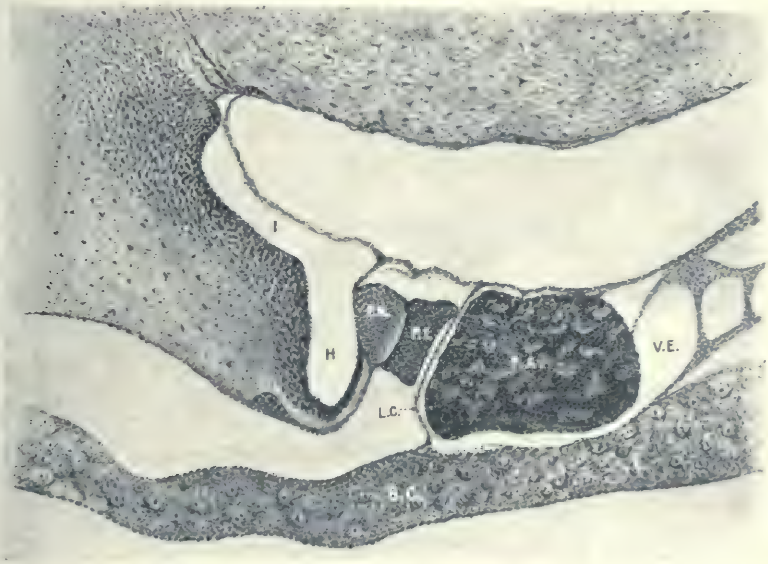

Fig. 28.

← Anterior direction.

Median sagittal section of the pituitary of the frog (*rana esculenta*). (*After Gentes.*) I, infundibular process; H, infundibular angle; PN, pars nervosa; PI, juxtaneural epithelium; PA, distal epithelium; LC, connective tissue separating two lobes; BC, base of cranium; VE, lymphatic vesicle.

Caudata.—In the *salamander* (*salamandra maculosa*) the pituitary has a very similar formation to that seen in the frog (fig. 29). There is, however, one important distinction, namely, the glandular epithelial elements of the pars anterior are arranged round blood-channels, as in the cases of some elasmobranchs (see fig. 25).

In amphibians, then, there are several points of importance: first, the small extent of the pars nervosa, which is merely formed by the wall of the hollow infundibular process abutting

[1] Gaupp, E., *Nervensystem. A. Ecker's und R. Wiedersheim's Anatomie des Frosches*, 1897, 94.

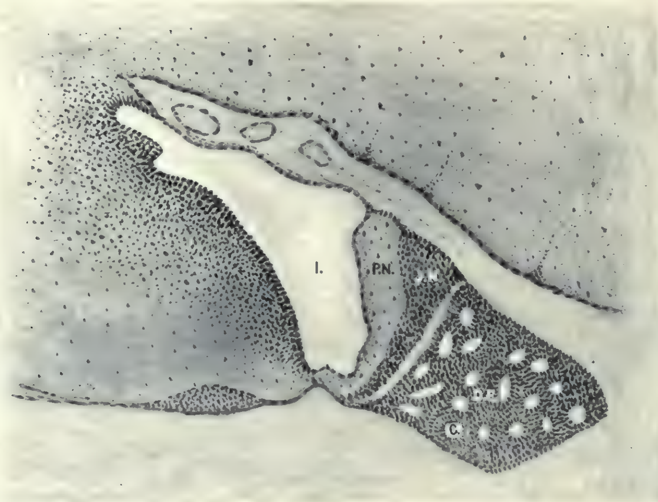

Fig. 29.

← Anterior direction.

Median sagittal section of the pituitary of the salamander (*salamandra maculosa*). (*After Gentes.*) I, infundibular process; PN, pars nervosa; JN, juxtaneural epithelium; DE, distal epithelium; C, capillary gland.

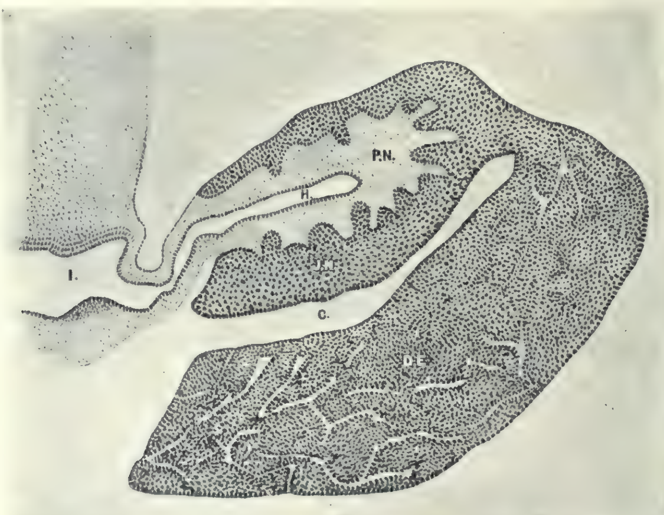

Fig. 30.

← Anterior direction.

Median sagittal section of the pituitary of the lizard (*lacerta viridis*). (*After Gentes.*) I, infundibular process; H, infundibular recess; PN, pars nervosa; JN, juxtaneural epithelium; DN, distal epithelium; C, residual cavity.

on the hypophysis; second, the well-defined but limited pars intermedia and the extensive distal epithelial portion in which the cells are closely related to its internal blood-supply.

REPTILIA

In some of the reptiles—*lacerta viridis* (Gentes, Herring); *alligator mississippiensis* (Tilney)—an arrangement similar to

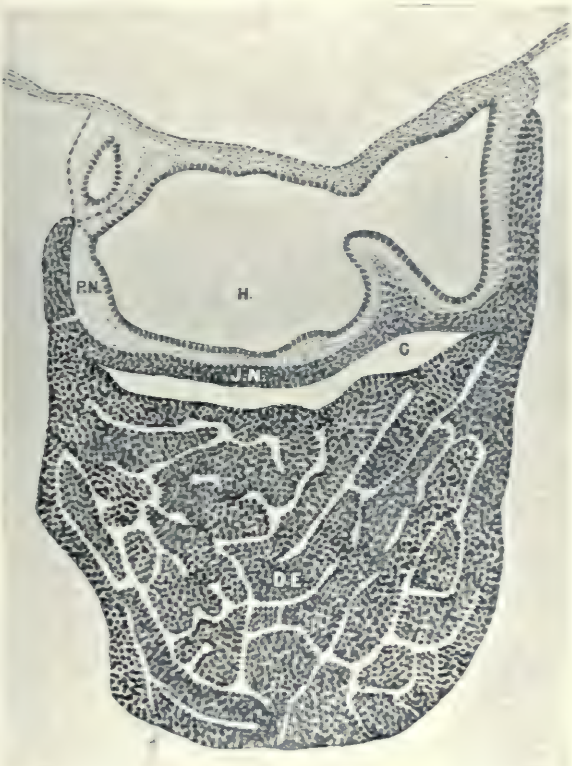

FIG. 31.

Median sagittal section of the pituitary of the tortoise (*testudo europœa*). (*After Gentes.*) H, infundibular recess; P.N. pars nervosa; J.N. juxtaneural epithelium; DE, distal epithelium; C, residual cavity.

that just described is found in regard to the pars intermedia and pars nervosa, but the ramifications of the latter are greater (fig. 30). In some reptiles the pars 'posterior' is superior to the pars 'anterior', which forms as it were, a saucer below it (fig. 31). We shall see that this cup-and-saucer arrangement

also obtains in some of the higher mammals. According to Tilney two types of cells are found in the pars anterior of the alligator—acidophils, which are centrally placed, and basophils at the periphery. The residual lumen or cleft is usually quite distinct.

In the *tortoise* (*testudo europæa*), according to Gentes, the pituitary is more like that seen in birds and mammals than is the case in most other reptiles. There is very little irregularity in the surface of the pars nervosa, and there is an anterior tongue of the distal epithelial portion (fig. 31).

Herring[1], also, has described the histological features of the reptilian (*testudo græca*) pituitary. He found that the distal epithelial portion is made up of numerous acini lined with cubical or columnar epithelium and filled with secretion.

AVES

Gallus domesticus.—In regard to the fowl, which has a type of pituitary common to many birds, investigators have not been entirely in agreement. Hannover[2] and Herring[3] state that the anterior lobe, which is in front of and below the posterior lobe (fig. 32), is made up of undifferentiated cells, and, in consequence, resembles parathyroid tissue. These cells are, they state, small and finely granular and are unlike the cells in the mammalian pituitary. On the other hand, Sterzi[4], Gentes[5] and Tilney[6] describe chromophil cells in the pars anterior. The last-named also describes basophils which, he says, are situated almost entirely on the anterior margin of the cleft; whereas, according to the same observer, the eosinophils occupy the rest of the pars anterior, some staining lightly, others darkly.

Herring was unable to find a cleft, but Tilney describes an " appreciable space or cavity ".

In passing, it may be noted that Tilney appears to consider

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1913, vi, 73.

[2] Hannover, A., *Recherches Microscopiques sur le System Nerveux,* 1844, 26.

[3] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 261.

[4] Sterzi, A. (quoted by Gentes), *Atti dell' Accad. Sci. Veneto-Trentino-Istriana,* 1904, i, 72.

[5] Gentes, L., *Soc. Sci. d'Arcachon, Travaux des laborat.*, Bordeaux, 1907, 129.

[6] Tilney, F., *Memoirs Wistar Instit. Anat. and Biol.*, Philadelphia, 1911 (No. 2), 1.

cells that would ordinarily be described as 'chromophobe' as 'basophil'.

I have myself examined the fowl's pituitary and have come to the conclusion that the divergence of opinion in regard to the character of the cells in the distal epithelial portion is due to the fact that different observers have examined pituitaries in different physiological states; that is to say, that if hens be examined the appearance of the pituitary will be found to vary

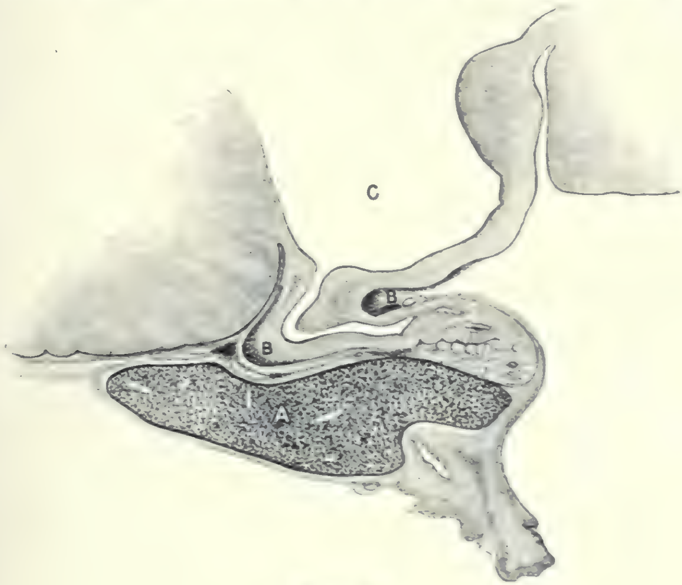

Fig. 32.

← Anterior direction.

Median sagittal section of the pituitary of the fowl (*gallus domesticus*). (*After Herring.*) A, distal epithelium; B, juxtaneural epithelium; C, third ventricle.

with the state of genital activity—a subject I shall discuss more fully in the appropriate place (p. 87).

In the cock and in the egg-laying hen I have found that the distal epithelial portions are very similar: there are many eosinophil cells, with small, round, dark nuclei, mixed indiscriminately with neutrophil cells having large nuclei which show a chromatin network—an average field (fig. 66A, p. 90) shows a kaleidoscopical disregard of order and arrangement. It is in the brooding state that the cells assume a uniform type, as we shall see later.

I have been unable to detect any cleft, but it is common to see in sections artificial separation of the distal epithelial cells from the neural process.

The pars nervosa in the fowl is convoluted and hollow, and opens into the third ventricle. The pars intermedia is very poorly developed, and is not spread uniformly on the pars nervosa; the neck, however, is thickly covered.

In this short survey of the morphology of the pituitary of creatures below the mammals several important facts have been recorded. First, in the elasmobranchs the pars posterior is not always present. Second, the cells of the pars anterior do not show acidophil and basophil differentiation in the lowest vertebrate forms investigated; and in some the cells are arranged in acini with capillaries in the lumina. Third, the pars nervosa when present usually shows a hollow, branched or convoluted arrangement; and, if we were to judge only by appearance, the close application of the pars intermedia cells to these hollow, branching processes, would lead us to the conclusion that the partes intermedia and nervosa together form a gland that discharges its secretion into the third ventricle.

All these points will lie before us later when an attempt is made to discuss the functions of the pituitary.

From this point we may continue our study of the comparative anatomy by a consideration of the pituitaries of representatives of different orders of mammals, some of which have repeatedly been described not only by the writers already named, but also by Lothringer[1], Trautmann[2] and many others.

It may be mentioned in the first place that there appears to be some relationship not only between the general contour of the pituitary, and the relative positions of the pars nervosa to the epithelial portions, but also between the general shape of the skull and the depth of the pituitary fossa. Thus we find that in long flat-headed animals, such as the dog (fig. 51) and the hedgehog (fig. 54), the pars nervosa is superior or superoposterior to the epithelial portions, and the fossa is shallow; whereas in the short-headed animals, such as the ornithorhynchus (fig. 33), the cat (fig. 47), the lemur (fig. 56), the monkey (fig. 59)

[1] Lothringer, S., *Arch. f. Mikr. Anat.*, 1886, xxviii, 257.

[2] Trautmann, A., *Arch. f. Mikr. Anat.*, 1909, lxxiv, 311.

and Man (fig. 60), the pituitary is situated in a deep fossa, and the pars nervosa is more directly posterior to the epithelial portions.

MAMMALIA

Monotremata.—Of the most primitive mammalian order (monotremata) only two species now exist—the echidna and the ornithorhynchus. I have had the opportunity of examining these animals; but my material in regard to the echidna was not sufficiently well preserved to enable me to make satisfactory histological examinations.

The pituitary of *ornithorhynchus anatinus* which has not, so far as I know, been described previously, is singularly interesting, in that it shows certain characteristics of the higher fishes and some reptiles with respect to the pars posterior. The organ is situated in a fairly deep fossa; consequently its outline is found to be roundly oval in shape. The pars anterior is round and convex in front and slightly concave behind. This posterior surface is separated by a cleft from the pars posterior which fits closely to it (fig. 33).

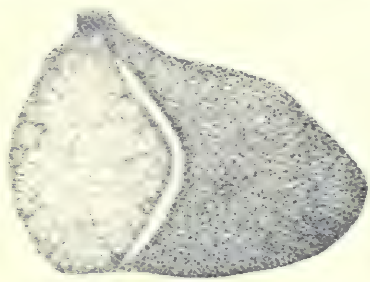

FIG. 33.

Anterior direction. →

Median sagittal section of the pituitary of *ornithorhynchus*. × 15.

The cells of the pars anterior are both chromophil and chromophobe. The former are for the most part finely granular and eosinophil; but here and there coarsely granular, spherical cells are to be seen, and these show gradations from a bluish-pink acidophilia to purple basophilia—variations that probably represent transitional phases from acidophilia to basophilia. The nuclei of the large dark cells are eccentric in position (fig. 34). The chromophobe cells are shrunken and ragged and have clear, lightly staining nuclei. Towards the infundibular stalk the cells, here and there, have an acinous arrangement. Granular secretion and colloid material, however, are very scarce.

There is a considerable amount of supporting tissue among the cells of the pars anterior, especially towards the periphery, where spindle-shaped, kite-shaped, and long triangular nuclei stand out prominently among the epithelial cells. Blood-spaces are to be seen, but they are not very conspicuous.

The cells of the pars intermedia of the ornithorhynchus entirely surround the pars nervosa in a thick layer; and from the cellular capsule columns of cells pass deeply down and even completely through the pars nervosa (figs. 35 and 36). These

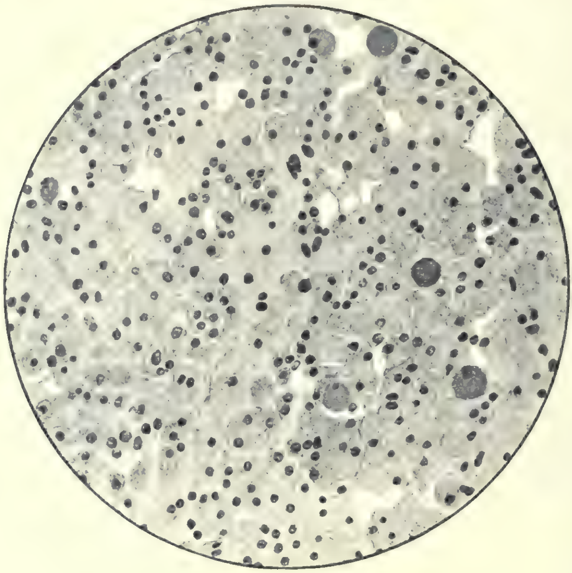

Fig. 34.

Section of the pars anterior of the *ornithorhynchus*.

× 250.

cells are polygonal in outline, are neutrophil in staining reaction and have rounded nuclei; they appear to have no supporting tissue. A few small masses of granular secretion are to be found among the cells, but there is no evidence of any vesicular formation.

The pars nervosa is peculiar in that not only is it channelled by the cells of the pars intermedia, but also it is divided up into lobules by fine, though dense, connective tissue trabeculæ, in which flattened nuclei may be seen. It is noteworthy, also, that the invading columns of cells of the pars intermedia pass down

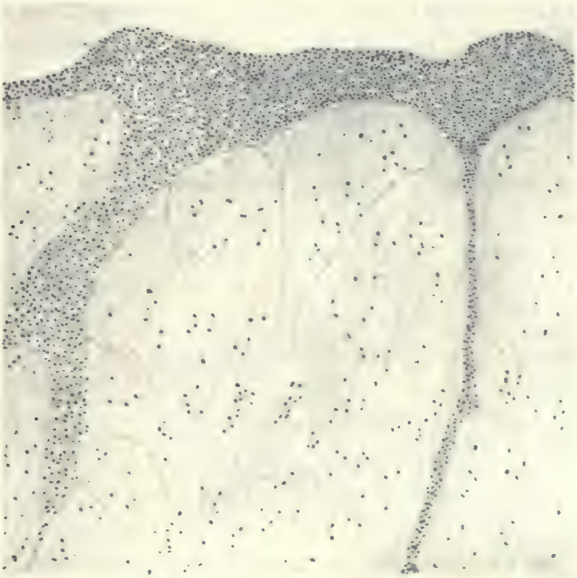

Fig. 35.
Section of the partes intermedia and nervosa of *ornithorhynchus*.
× 60.

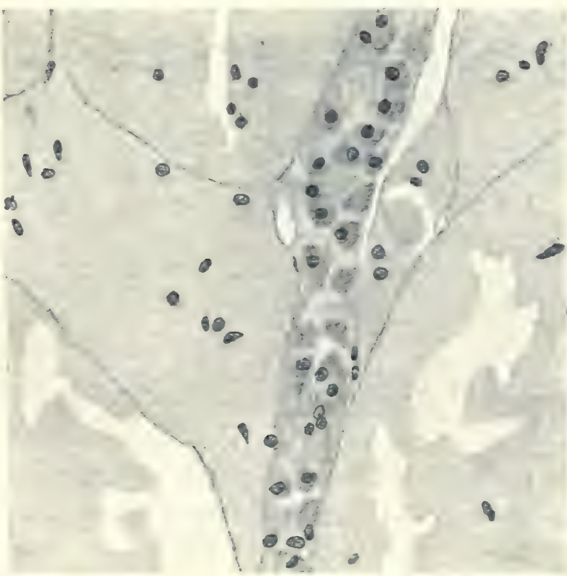

Fig. 36.
Section of the pars nervosa of *ornithorhynchus*, showing a column of pars intermedia cells passing down.
× 400

channels defined on either side by a layer of thin, tough connective tissue (fig. 36). There is distinct evidence, too, that those trabeculæ which do not enclose ingrowing columns of intermedia cells are nevertheless channels; that is to say, the connective tissue is composed of two separate layers. There is, occasionally, some secretion to be found among the epithelial cells enclosed in the trabeculæ, and not infrequently these cells migrate and invade the neuroglial tissues proper, and even give rise to the formation of the so-called 'secretion-bodies'.

As already stated, this invasion of the pars posterior by columns of juxtaneural epithelium recalls the branching arrangement of the pars nervosa seen in many fishes and reptiles; and it represents, no doubt, a structural arrangement whereby an intimate and extensive relationship is established between the pars intermedia and pars nervosa.

Marsupialia.—The pituitary of the marsupial has been described by Tilney[1] in the case of the opossum (*didelphys virginiana*). I, also, have examined the pituitary of this animal.

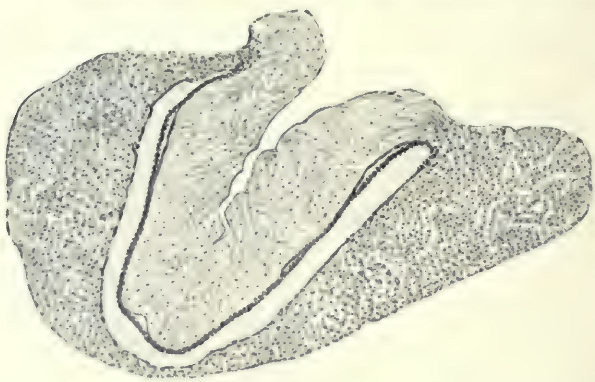

FIG. 37.

Median sagittal section of the pituitary of the opossum (*didelphys virginiana*). × 15.

The pars nervosa is situated superiorly, or slightly superoposteriorly, to the distal epithelial portion (fig. 37). Tilney describes a central cavity in the pars nervosa and a lumen through the stalk leading to the third ventricle. In the specimen examined by me—an old male—there is a slit-like central cavity.

[1] Tilney, F., *Memoirs Wistar Instit. Anat. & Biol. Philadelphia*, 1911 (No. 2), 1.

The pars nervosa is composed of neuroglial elements arranged in a peculiar manner; that is to say, there is a dense band folded on itself like the lutein-layer in the ovary. Between the folds the neuroglial elements are loose. It is possible that the convoluted band is the remains of the edge of a large cavity lined with ependymal cells, which existed in an early stage of development.

The juxtaneural epithelium entirely surrounds the pars nervosa, and is for the most part composed of one layer only of

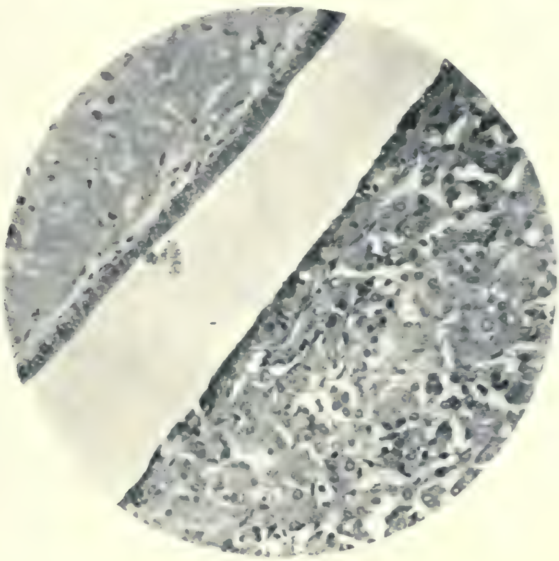

Fig. 38.

Section of the pituitary of the opossum (*didelphys virginiana*), showing the distal epithelium, below and to the right, separated by the cleft from the pars nervosa which is covered with a single layer of juxtaneural epithelium. (*Photomicrograph.*) × 250.

columnar epithelium, the cells of which have large, oval, central nuclei. Here and there the epithelial investment may be two or three cells in depth, but this is quite exceptional. Tilney, however, describes a layer several cells thick. But in the specimen examined by me the uniformity of the single-cell layer was remarkable and interesting (fig. 38). The cells of the juxtaneural epithelium are neutrophil.

The distal epithelial portion is separated from the rest of the organ by a wide cleft; and those cells which abut on this

residual lumen are flattened on the surface and are tightly packed together (fig. 38).

The distal epithelium is abruptly divided into two parts by differences in the staining affinities of the cells. In the anterior portion the cells are uniformly lightly basophil or chromophobe. The smaller cells have darkly staining nuclei, and the larger cells clear, round, central nuclei. In the posterior portion brightly staining eosinophil cells with small dark nuclei are mixed indiscriminately with large chromophobe cells containing large, round, clear nuclei.

The cells of both parts of the distal epithelial portion are arranged in irregular branching columns. There are numerous blood-spaces, but there is very little intercellular connective tissue.

Tilney has described dark basophils and colloid secretion in this part of the pituitary of the opossum. I have been unable to find either darkly staining basophil cells or colloid material.

Ungulata.—The commoner domestic species—the ox, the pig and sheep—have probably been examined by numerous observers, but there are very few accounts of the pituitaries of the sheep and pig.

The pituitary of the *ox* (*bos taurus*) has been described by Lewis, Miller and Matthews[1], by Herring[2] and others.

The whole gland is oval and is placed in a deep fossa with a narrow outlet for the infundibular stalk. The anterior lobe is oval and is separated from the posterior lobe by a cleft. The pars posterior is crescentic in shape—the concave aspect abutting on the cleft (fig. 39). The front, the lateral and the lower aspects of the pars nervosa and the entire circumference of the neck, are covered with cells of the pars intermedia, which consists of a layer many cells deep. This layer is thickest at the bottom and in the middle of the cleft (fig. 39). The pars nervosa is solid, and there is no invasion or dipping down of the pars intermedia, which forms an unbroken line.

The anterior lobe is made up of brightly staining eosinophil cells, mixed indiscriminately with chromophobe, or faintly basophil, cells. No dark basophils are to be observed. The general

[1] Lewis, D. D., J. L. Miller and S. A. Matthews, *Amer. Arch. Med.*, 1911, vii, 785.

[2] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1914, viii, 245.

arrangement of the cells is more or less acinous; but little or no colloid material is to be found.

The pars intermedia consists of the usual faintly basophil cells which may assume an acinous arrangement near the neck. A striking feature of the pars intermedia in this animal is the number of large blood-vessels lying among the epithelial cells. The pars nervosa presents the same characteristic in regard to the blood-vessels, which are extremely numerous and large (fig. 40). In no other pituitary that I have examined has there been such a profusion of vessels through the whole of the nervous process.

FIG. 39.

Median sagittal section of the pituitary of the ox (*bos taurus*). × 7·5.

I have been unable to find secretion-bodies in the pars nervosa. Herring states that "they are very pronounced"; but Lewis, Miller and Matthews assert that they are not a common phenomenon.

The pituitary of the *sheep* (*ovis aries*) has been described by Peremeschko[1] and Tilney[2]. I, also, have examined this organ.

It is stated by Tilney that the "hypophysis"—presumably the pars anterior—of this animal is divided and subdivided by "a rich trabecular system" which gives it "the semblance of a lobulated organ"[2]. Tilney also states that the

[1] Peremeschko (no initial in original), *Virchow's Arch.*, 1867, xxxviii, 329.

[2] Tilney, F., *Memoirs Wistar Instit. Anat. and Biol.*, Philadelphia, 1911 (No. 2), 1.

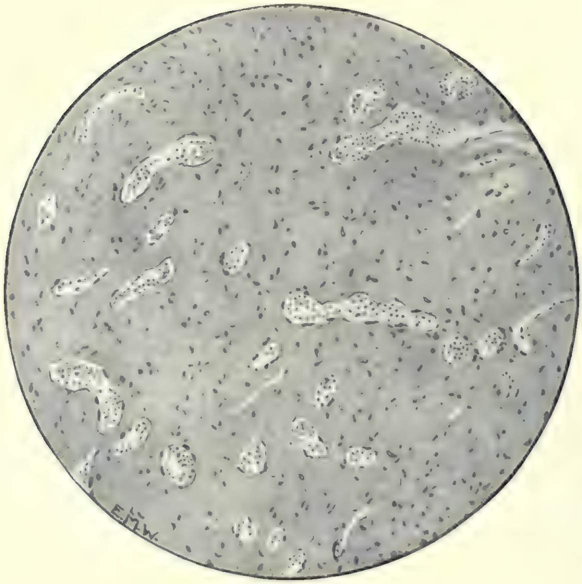

Fig. 40.

Section of the pars nervosa of the ox (*bos taurus*), showing many blood-vessels containing blood.

× 100.

Fig. 41.

Median sagittal section of the pituitary of the sheep (*ovis aries*). The small neural process is seen to the left of the picture.

× 7·5.

pars anterior is composed chiefly of eosinophil cells, each of which appears to have its definite place in the wall of a vesicle.

There is no doubt that the pars anterior, especially at the inferior periphery, is subdivided into lobules by wide spaces (fig. 41). I think there is no doubt that these are blood-channels, for they are lined with endothelium (fig. 42).

There is a rich vascular system, and the epithelial cells are arranged in a radial fashion around the sinuses (fig. 43).

The eosinophils are certainly most prominent, but there are

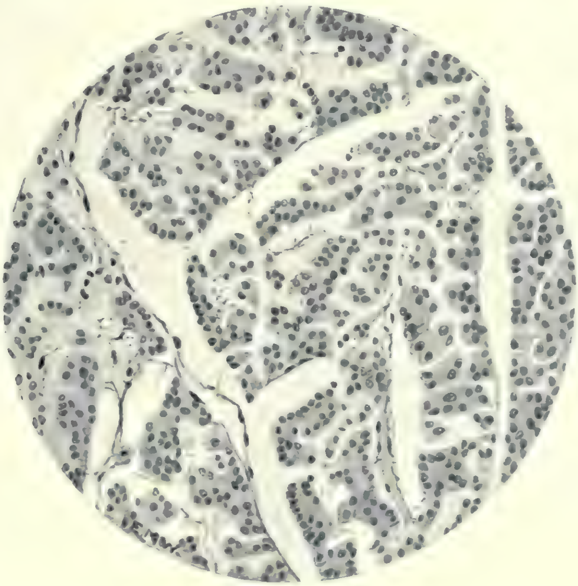

FIG. 42.

Section of the distal epithelial portion of the sheep (*ovis aries*), showing spaces lined with endothelium.

× 150.

many faintly basophil, or neutrophil, cells which are often found in large masses.

The pars intermedia, which shows the usually faintly basophil staining affinity, is many layers in depth, and invests the pars nervosa in front and at the sides, and surrounds the stalk. The cells are arranged in columns radiating from the surface of the pars nervosa, and there is much supporting tissue. Colloid secretion may be found in the cleft.

The pars nervosa, which is solid, is very small, and I have

been unable to find blood-vessels, except in close relation to the pars intermedia.

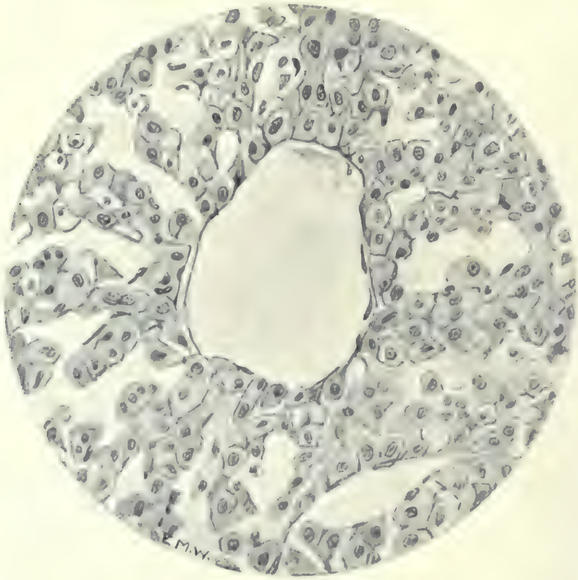

FIG. 43.

Section of the distal epithelial portion of the sheep (*ovis aries*), showing radial arrangement of the cells around a blood-channel.

× 375.

I have, also, examined the pituitary of the *pig* (*sus domesticus*). In this animal the organ is a long oval in shape (fig. 44). The anterior lobe is bluntly rounded anteriorly, and is slightly concave behind to accommodate the pars posterior which is pear-shaped, and is separated from the pars anterior by a cleft.

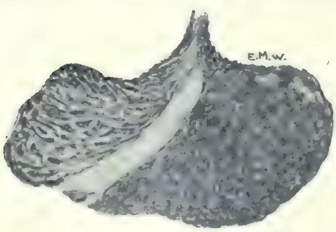

FIG. 44.

Median sagittal section of the pituitary of the pig (*sus domesticus*).

× 7·5.

The pars nervosa is entirely surrounded by the pars intermedia, which however does not form a thick layer except in the neighbourhood of the cleft and around the stalk, which is entirely covered.

The pars anterior has histological features exactly similar to those already described in regard to the pituitary of the ox.

The pars intermedia shows the usual staining reaction. Here

and there wedge-shaped masses of cells dip down a short way into the underlying pars nervosa.

The pars nervosa shows a peculiar whorled arrangement of the fibres, the general trend of which is towards the stalk. A number of blood-vessels is to be observed in this structure, but not so many as in the case of the ox. A few granular bodies may be seen in the neighbourhood of the pars intermedia.

Rodentia.—Tilney[1] states that in rodents generally, the pars nervosa lies above the rest of the pituitary. Such, however, is certainly not the case in the guinea-pig and the rabbit.

This author also states that in the *rat* (*mus decumanus*) the cells of the distal epithelial portion are basophil in the neighbourhood of the narrow cleft, and eosinophil in the rest of the distal epithelial portion, and that the juxtaneural epithelium forms a deep layer of faintly basophil cells. In my experience, however, deeply staining basophils are not seen in the pars anterior of the *rabbit* (*lepus cuniculus*), the *guinea-pig* (*cavia familiaris*) or the *dormouse* (*muscardinus avellanarius*), nor is granular secretion or colloid material to be observed. Faintly basophil—really chromophobe—cells are fairly numerous, but most of the epithelial cells of the pars anterior are lightly eosinophil.

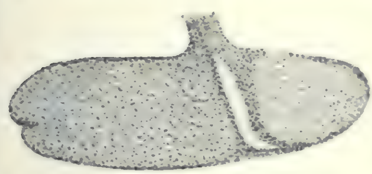

FIG. 45.

Median sagittal section of the pituitary of the guinea-pig (*cavia familiaris*). × 15.

In the *guinea-pig* the whole pituitary is somewhat elongated, and there is a well-defined cleft (fig. 45). In the *rabbit* the cleft is extremely narrow, so much so that the very regular and thick pars intermedia appears to lie almost directly on the pars anterior (fig. 46).

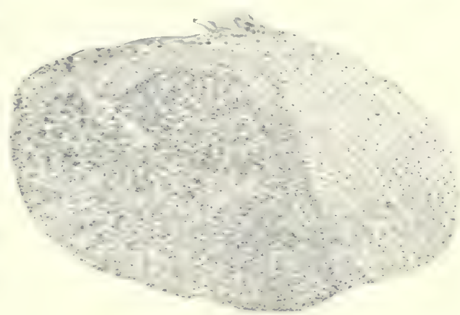

FIG. 46.

Median sagittal section of the pituitary of the rabbit (*lepus cuniculus*). × 15.

[1] Tilney, F., *Memoirs Wistar Instit. Anat. and Biol.*, Philadelphia, 1911 (No. 2), 1

The pars intermedia (juxtaneural epithelium) thickly covers the pars nervosa. These cells stain faintly with basic dyes—a staining reaction that is universal in regard to the cells of the pars intermedia of all mammals.

Carnivora.—Of this mammalian order the two most commonly investigated types are the domestic *dog* (*canis familiaris*) and *cat* (*felis domestica*). These animals, however, present in their pituitaries widely different characteristics.

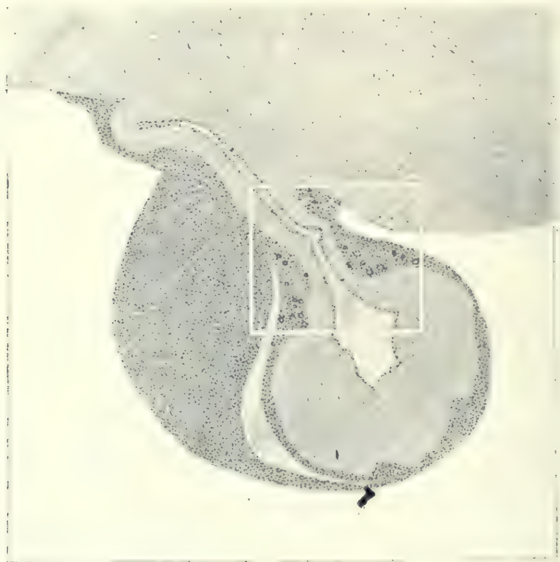

FIG. 47.

Median sagittal section of the pituitary of the cat (*felis domestica*). The part enclosed in the white lines is shown more highly magnified in figure 48. × 15.

In the *cat* the pituitary is situated in a very deep fossa; consequently the pars nervosa is placed posteriorly, and the whole organ is almost round in shape (fig. 47). Probably the best description of this pituitary has been given by Herring[1], who has directed special attention to the hollow space to be found in the pars nervosa and the opening through the neck which connects the cavity with the third ventricle. This space and the channel are lined with ependymal cells. Curiously, no

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.

mention is made of this cavity by Tilney in his description of the cat's pituitary, and his account is singularly poor in other respects, for, contrary to his statement, there is usually a considerable amount of secretion in the particularly well-developed acini in the neighbourhood of the neck (fig. 48). This acinous formation often extends along the base of the brain, under the third ventricle, in a most definite manner; and the acini, in this region, are widely separated from one

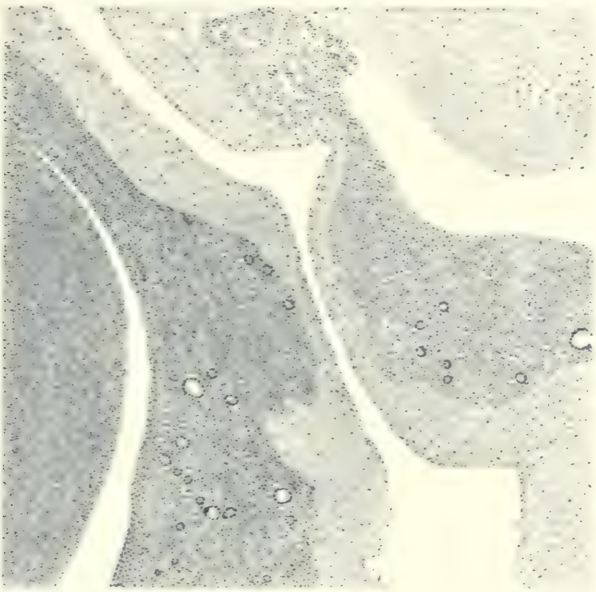

FIG. 48.

Section of the pituitary of the cat (*felis domestica*), showing more highly magnified the part enclosed in white lines in figure 47.

× 50.

another by an exceeding vascular connective tissue stroma (fig. 49).

The juxtaneural epithelial cells (pars intermedia) in the cat completely surround the pars nervosa and the neck, and in some places the cells form wedge-shaped masses projecting inwards (fig. 47). These juxtaneural cells stain rather more deeply than usual with the basic dyes. Supporting spindle-shaped cells are always found in this situation (fig. 50).

The pars anterior is extremely vascular, and the epithelial

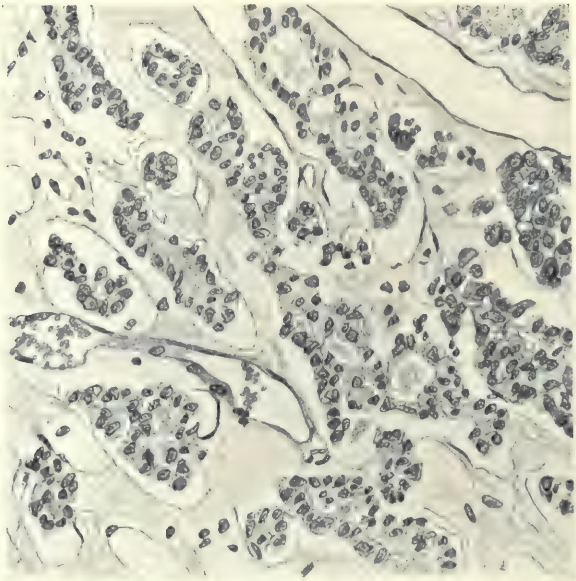

Fig. 49.

Section of the reticulated portion of the pars intermedia of the cat (*felis domestica*), showing the vesicular arrangement of the cells which are lying in a loose connective tissue stroma containing large blood-vessels.

× 250.

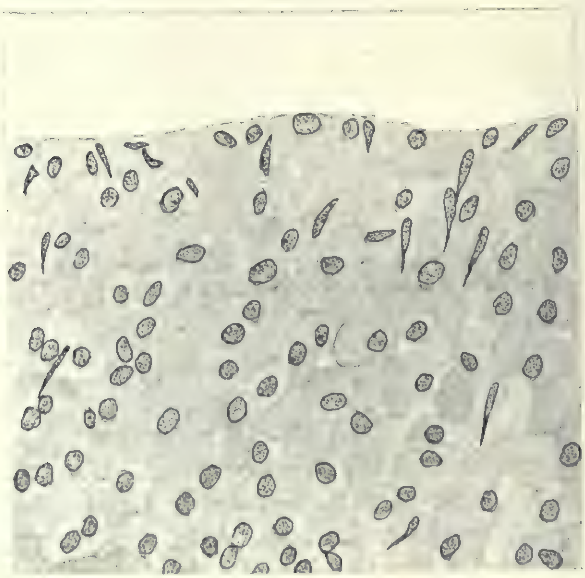

Fig. 50.

Section of the pars intermedia of the cat (*felis domestica*) where it abuts on the cleft, showing supporting spindle-shaped cells.

× 700.

cells form either an arrangement of short branching columns, resembling the disposition of heart-muscle, or a more distinctly acinous grouping. The cells are for the most part eosinophil, but many show a hazy, moderately deep basophilia, and it is not uncommon to see groups of quite definite basophils, although their colour-affinity is not so pronounced as in the human subject. Here and there, granular secretion may be found among the acini. Pale chromophobe cells with large, clear nuclei are plentiful. As in practically all mammals in which the pars intermedia is well developed, the cells of the distal epithelial part bordering on the cleft are closely packed and resemble the cells of the juxtaneural epithelium in appearance and staining reaction.

FIG. 51.

Approximately median sagittal section of the pituitary of the dog (*canis familiaris*). The part enclosed in a white ring is shown more highly magnified in figure 52. × 15.

In the pars nervosa of this animal the so-called 'secretion-bodies' are frequently seen. The importance of these bodies will be discussed later (p. 97 and following).

In the *dog* the pituitary is situated in a very shallow fossa at the base of the skull; consequently the pars nervosa lies superiorly to the epithelial portions. The pars nervosa is solid, but there is a slight ventricular depression in the neck. There is a wide, irregular residual lumen or cleft, and the pars intermedia covers unevenly the whole of the neural process, while the distal epithelial part extends below the cleft like a saucer, with the largest mass of cells anteriorly (fig. 51).

The 'anterior' lobe is very vascular and there is but little supporting tissue. The cells are arranged in cords, and are, for the most part, faintly staining both with acid and basic dyes, more especially with the acid.

Where the cells of the pars 'anterior' merge with those of the pars intermedia they assume a more acinous arrangement, become faintly basophil and secrete a granular substance. I have not found the deeply staining basophils, in specific areas in the distal epithelial portion, as described by Tilney[1].

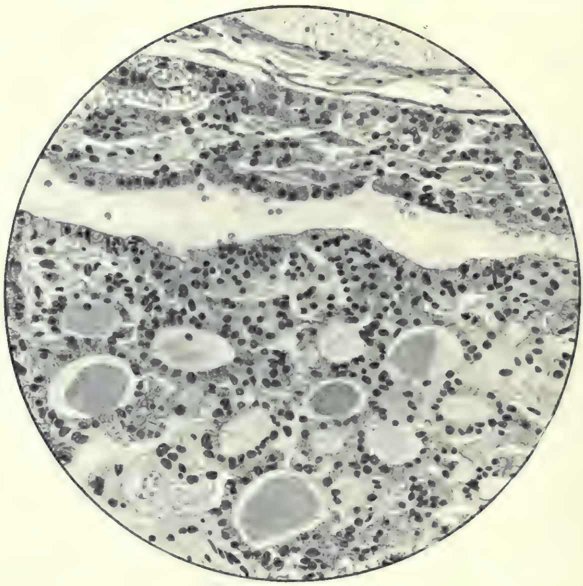

FIG. 52.

Section of the pars intermedia of the dog (*canis familiaris*), showing more highly magnified the part enclosed in a white ring in figure 51. × 200.

The cells of the juxtaneural portion are very interesting in this animal. As is shown in figure **51**, they invest completely the pars nervosa and form wedges dipping into it, as in the cat. A peculiar feature, also, in this animal is the extensive acinous arrangement of the pars intermedia which is found in every part of it, and on either side of the cleft at the neck (fig. 52). In no other animal that I have examined, not excepting the cat, is so much secretion found, not only in the

[1] Tilney, F., *Memoirs Wistar Instit. Anat. and Biol.*, Philadelphia, 1911 (No. 2), 1.

epithelium applied to the pars nervosa, but also in that which is distant from the cleft—in what may be described as the reticulated portion of the pars intermedia. In this last mentioned area the granular, faintly basophil secretion is found not only in the acini but also quite indiscriminately in diffuse masses among the cells (fig. 53). No mention is made of this secretory activity of the pars intermedia of dogs by Tilney.

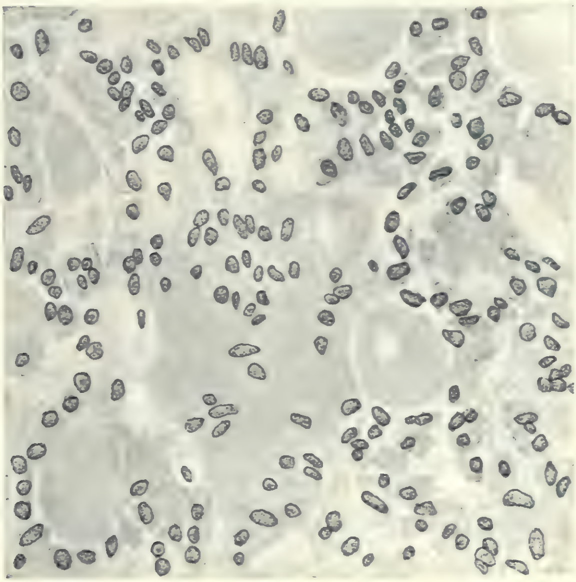

Fig. 53.

Section of the pars intermedia of the dog (*canis familiaris*), showing secretion diffused among the cells.

× 500.

Insectivora.—I have examined pituitaries from the *hedgehog* (*erinaceus europæus*)—hibernating and non-hibernating—but have found no other description in the literature.

The organ is very flat and lies in a very shallow depression in the base of the skull; consequently the pars nervosa lies superiorly to the epithelial portions (fig. 54). There is a definite cleft (residual lumen) which is placed below the pars 'posterior', or pars superior as it really is. The pars nervosa is solid, and is covered with a nearly even layer of pars intermedia, lying from four to eight cells deep.

In the non-hibernating animal—the phenomenon of hibernation will be discussed presently (p. 85)—we find that in the distal epithelial portion the cells are arranged in an acinous

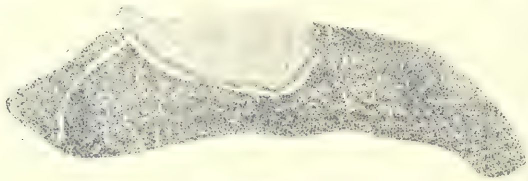

FIG. 54.

Anterior direction →.

Median sagittal section of the pituitary of the hedgehog (*erinaceus europæus*). × 15.

manner. The cells are of three types: first, finely granular, lightly eosinophil cells with large, round, faint nuclei are found to be the most numerous; second, many deeply eosinophil coarsely

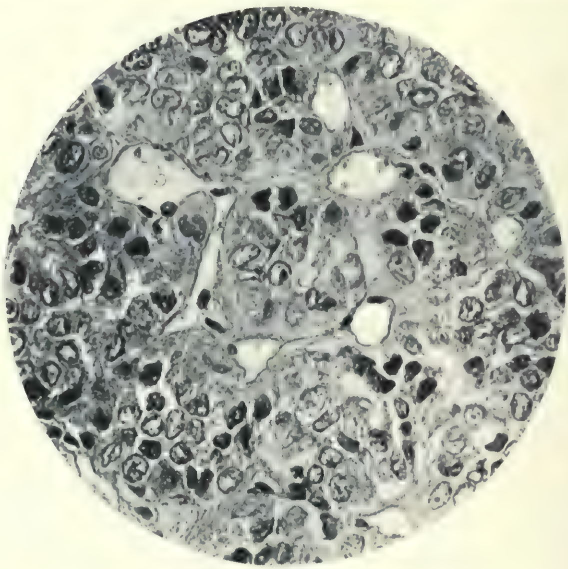

FIG. 55.

Section of the distal epithelial portion of the hedgehog (*erinaceus europæus*), showing irregularly shaped, darkly staining nuclei. (*Photomicrograph.*) × 500.

granular cells with peculiar very darkly staining—almost mahogany-coloured—nuclei of irregular shape (fig. 55); third, a few chromophobe, or faintly basophil, cells with large clear

nuclei—a familiar characteristic of this type of cell—may be seen. Blood-vessels and blood-spaces are very numerous, and there is a considerable amount of supporting connective tissue.

The cells of the pars intermedia (juxtaneural) resemble very closely the cells of the distal epithelial portion, being for the most part faintly basophil and having large clear nuclei; yet here and there eosinophil cells with dark nuclei are to be found—a most unusual phenomenon. There are numerous large blood-vessels immediately below the cells of the pars intermedia among which are to be seen a few supporting spindle-shaped cells.

It will be noticed that in figure 54 the cleft extends downwards posteriorly into the cells of the distal epithelium. The cells on the posterior aspect of this extension resemble those of the juxtaneural epithelium.

Primates: *Lemuridæ.*—Next in an ascending scale we may consider the *lemurs*, which, possibly, represent the common ancestors of the higher apes and man.

Of this family, I have examined the ring-tailed lemur (*lemur catta*), which is nocturnal in its habits. I have been unable to find any account of the hormonopoietic organs of this animal in the literature.

Before describing the pituitary, I may mention that in the animal examined (only one living specimen was obtained) the thyroid resembled in its histological features that seen in exophthalmic goitre in human subject. This interesting fact becomes more striking when it is remembered that the animal has a natural condition of exophthalmos, possibly to enable it to see well when roaming about at night.

The structure of the pituitary, too, shows peculiarities for which it is difficult to account.

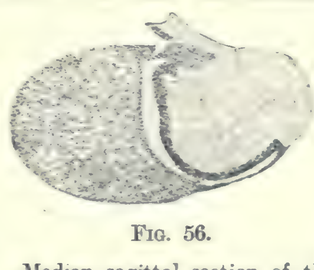

FIG. 56.

Median sagittal section of the pituitary of the lemur (*lemur catta*). × 10.

In the lemur this organ is situated in a deep fossa; consequently it is oval in shape, and the pars nervosa is situated posteriorly (fig. 56). The cells of the pars intermedia cover the pars nervosa in front, beneath and at the sides, and in front of the stalk. Where these cells are applied to the body of the pars nervosa, which is

solid, they show a tendency to dip down, and appear to form islets of cells, as shown in cross-section, among the neuroglial elements (fig. 57). The pars intermedia cells stain rather more deeply with basic dyes than is usual in mammals—except, perhaps, in the cases of the dog and cat. Numerous supporting cells are found among the epithelial elements in this region, and groups of cells are enclosed by dense connective tissue.

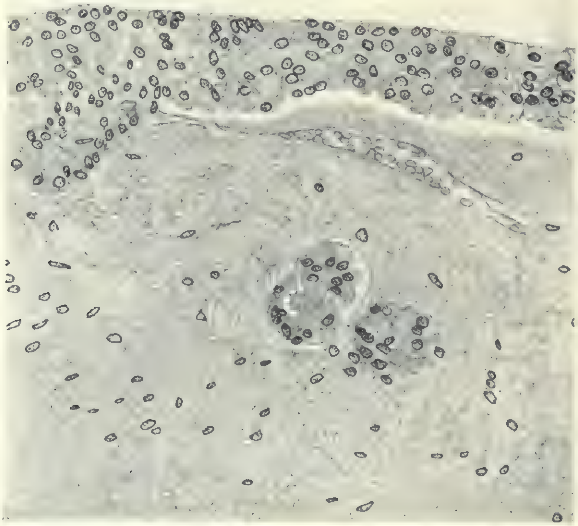

Fig. 57.

Section of the pars posterior of the lemur (*lemur catta*), showing apparent islets of pars intermedia cells in the pars nervosa.

× 250.

The pars anterior in the animal under consideration shows most pronounced and interesting features. The eosinophil elements are very bright and prominent, and in places are arranged in branching columns after the manner of heart-muscle. The only other type of cell seen is the active chromophobe cell (fig. 58). These chromophobe cells are large, stain very faintly with basic dyes, and appear to be almost confluent in places. This pseudosyncytial appearance of chromophobe cells was first described by Lannois and Mulon[1] as occurring in pregnancy; it

[1] Lannois, P. E., and P. Mulon, *Compt. Rend. de Soc. Biol.*, 1903, i, 448.

is also seen in pathological conditions—notably after removal of the thyroid—indeed, plate 4 (facing p. 187), showing the effect

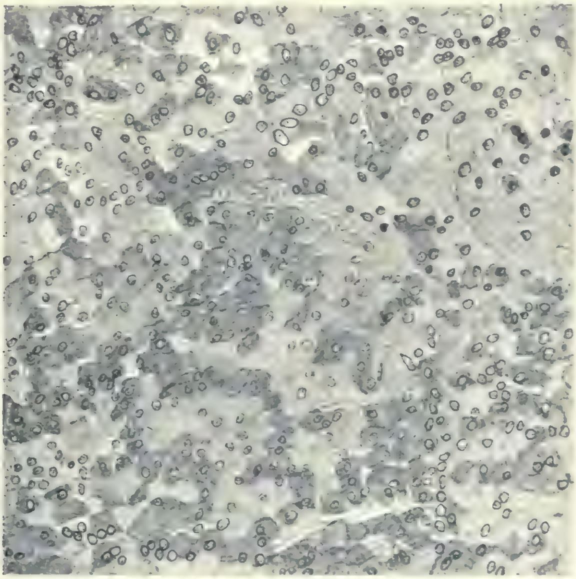

Fig. 58.

Section of the pars anterior of the lemur (*lemur catta*), showing dark eosinophil cells and light chromophobe cells.

× 250.

on the pars anterior in the cat of experimental removal of the thyroid, almost illustrates the normal appearance seen in the lemur examined, which was a young non-pregnant female. This phenomenon is curious when considered in conjunction with what has already been said about the structure of the thyroid in this animal.

Fig. 59.

Median sagittal section of the pituitary of the monkey (*macacus rhesus*).

× 10.

Simiidæ. — In *monkeys* the pituitary is situated in a deep fossa; it is, therefore, roundly oval in shape, and the pars nervosa is posterior in position (fig. 59). It is

probable that the pituitaries of the different species are very similar. I have examined *macacus rhesus*. Herring[1] and Tilney[2] also have examined this organ in monkeys. Tilney examined the baboon (*cynocephalus babuin*), but Herring does not state the species described by him.

The pars intermedia forms an investment varying in depth, but usually thin, over the front and sides of the pars nervosa and along the front, and, in some cases, around the stalk.

The pars nervosa is solid, and is comparatively large (fig. 59).

The pars anterior appears to be composed chiefly of eosinophil cells, although some faintly basic staining—really chromo-

FIG. 60.

Median sagittal section of the human pituitary. × 5.

phobe—cells may be seen. My observations coincide with those of Herring rather than with those of Tilney, in regard to the absence of basophils; but this may be explained by the fact that Herring and I examined the same species, while Tilney examined a species that may differ from *macacus rhesus*. Blood-spaces are numerous, but there is little other supporting tissue. The cleft is very narrow, and in this respect and in the limitation of the pars intermedia the pituitary of the monkey approaches in appearance that seen in *Man* (fig. 60), in whom the pars intermedia is of very slight extent, as already described.

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.
[2] Tilney F., *Memoirs Wistar Instit. Anat. and Biol.*, Philadelphia, 1911 (No. 2), 1.

In this brief study of the comparative features of the pituitary a few facts stand out as being of considerable importance. Their importance is related to the elucidation of the physiological functions of this organ.

We have found in one of the lowest vertebrates the complete absence of a pars nervosa ; we have observed its sudden development to, apparently, an organ of considerable physiological significance, if we may attach functional importance to morphological structure, which is, however, always a dangerous procedure. In bony fishes the maximum surface of nervous tissue is exposed, by a series of branching processes, to the epithelial covering ; and this phenomenon obtains to a considerable extent in reptiles and even in the monotreme mammals. Then, apparently, this feature disappears, except for the evidence of epithelial ingrowths in the pars nervosa, such as are seen in the cat and lemur. In the opossum and in the cat we find another interesting morphological characteristic, namely, a cavity within the pars nervosa which is continuous with the third ventricle ; and this has been held by Herring[1], Cushing[2] and others to constitute a factor of prime importance from a physiological point of view. In the amphibians and ungulates we have seen that blood-vessels are very numerous in connexion with the pars posterior. This, too, may be a point of some moment in regard to the physiology of this part of the pituitary.

We have, moreover, observed that the histological evidence of activity of the pars intermedia differs in different mammals, and that it appears to be greatest in the cat and dog so far as the actual production of an obvious secretion is concerned. In the monkeys and in Man the pars intermedia and the pars nervosa appear to be of small significance.

The comparative structure of the pars anterior likewise affords us some food for reflexion. In certain fishes and reptiles the cells are arranged in acini with blood-vessels in the lumina —a disposition which facilitates the passage of the secretion of the cells directly into the blood-stream. In no case do we see quite so well-defined a differentiation in eosinophils, basophils and chromophobes as in the normal pituitary of Man. There is, however, no doubt that in the lower vertebrates differentia-

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121, 161.

[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

tions do exist, but they are not pronounced in most of the mammals, nor, indeed, in Man till puberty. In the lemur there are extremely interesting histological features which we shall discuss again later, for use will be made of this comparative study in discussing the peculiar problems associated with the physiology and pathology of the pituitary.

PART II

THE PHYSIOLOGY OF THE PITUITARY

PART II

THE PHYSIOLOGY OF THE PITUITARY

In order to obtain information concerning the normal functions of an organ, we have definite and well-recognized methods of investigation. These are either purely physiological or pathophysiological; and before proceeding to discuss the application of them to the study of the pituitary body it will be useful to summarize the methods themselves.

I. Physiological Methods

(*a*) **Histological investigations.**—These enlighten us as to the nature of the structure with which we have to deal, and also enable us to discern the character of its functional processes in various circumstances. We learn by differential staining the chemical affinities of the different cells of the tissues investigated, and the various phases of their activity.

(*b*) **Chemical examination of the body-tissues and excreta.**—By this means we are sometimes able to discover the chemical nature of a secretion, and to trace in the blood or other body-fluids its rate of production and disappearance.

By this method, also, we are able to observe changes in the metabolism.

(*c*) **Injection, absorption, and ingestion experiments.**—In these investigations extracts of the organ concerned are introduced into the body of the experimental subject, and observations are then made in the following ways in regard to the immediate and remote effects produced.

i. *Immediate effects* of injections are noted by means of various physiological recorders; of absorption by placing the structures to be tested in Ringer's solution containing the extract, and by means of the implantation of freshly excised organs.

ii. *Late effects* of daily injections or ingestions into a previously normal animal, are noted in regard to the metabolism and to the structure of various other organs.

It is generally conceded that these methods of investigation are open to few objections ; but we must bear in mind that in our experiments under the third heading we are usually exhibiting quantities of an organic extract considerably in excess of those which the animal could receive from the same organ in normal circumstances and in the same period of time.

II. Pathophysiological methods

(*a*) **Operative procedures.**—i. *Partial or complete extirpation, destruction or injury of the organ* in situ.—There is no doubt that partial or complete extirpations are greatly to be preferred to destruction with the cautery and with other agents ; for it is difficult with destructive methods to limit the amount of necrosis effected, or to estimate the damage done to adjacent portions of the organ and the surrounding tissues. By extirpation experiments we are able to produce cessation of, or insufficiency in, the functions of an organ.

ii. *Extirpation or destruction followed by substitution therapy by means of injections, feeding, or grafting.*—By these means we are often able to learn whether our deductions, based on extirpation or destruction alone, are correct, for substitution may mitigate the effects produced. By this method of investigation, however, positive results alone are of value.

iii. *Stimulation of the organ* in situ.—This is accomplished by electrical impulses applied indirectly through the functional nerves, or by electrical currents or other methods of irritation, such as the pressure of a foreign body, applied directly ; also, by the injection of exciting substances (hormones) into the circulation.

(*b*) **Removal of, or injury to, correlated organs.**—In this way we may become acquainted with the relationships between various structures, such as the organs of internal secretion.

(*c*) **Injection of bacteria or toxins into the blood-stream,**

peritoneal cavity or subcutaneous tissues.—By this method, which, possibly, is a form of stimulation, we learn the behaviour of the organ to infections or toxæmias—a matter requiring consideration apart from stimulation by hormones.

(*d*) **Interpretation of pathological processes affecting the normal physiology of the organ concerned.**—Many pathological processes in an organ give rise to excessive or diminished function in varying degrees. From these so-called ‘ experiments of Nature ’ the physiologist may find much evidence to support or disprove conclusions reached in other ways.

In these methods, then, if they be properly carried out, we have the means of investigating fairly completely the functions of an organ such as the pituitary body. It will be obvious, moreover, that sometimes combined experiments, such as those described above under II (*a*) ii, may be especially useful; and in this connexion it must be pointed out that the full appreciation of the results of many of the methods mentioned depends on the completeness of the investigation. For instance, in extirpation experiments we must not be satisfied with observing whether the animal dies or survives ; we must learn, if possible, the actual effect of the experiment on the correlated organs and structures, and on the metabolism generally. Unfortunately, this completeness of investigation is rarely possible to the ordinary investigator, for he is not usually an expert in surgery, histology, chemistry and general medicine, and at the same time able to devote his whole time to experimental work ; and, on the other hand, the pure physiologist is not always sufficiently acquainted with the technique of surgery, and with the possible applications of his results to medical and surgical practice. It is, therefore, at present only by combining the results of many workers that we are able to view a subject such as that which we are at present discussing from a more or less comprehensive standpoint. No doubt the time will come when hospital laboratories will be established in this country in which *complete investigations* can be carried out under the same roof by the combined efforts of many workers, each of whom is a specialist in his own sphere of action.

§ i. PHYSIOLOGICAL INVESTIGATIONS

HISTOLOGICAL OBSERVATIONS

In its histological features the pituitary body is one of the most puzzling structures in the animal organism. It has, therefore, been the subject of much careful study; and however imperfectly we can connect the physiological functions with the special structure, we are at least now thoroughly familiar with the latter in the human adult. Nevertheless, a careful investigation into the differences seen at the different periods of life is urgently needed; for, although it may be possible for an experienced observer to recognize the pituitary of the child by the comparative uniformity in the staining reactions of the cells of the pars anterior, and that of elderly persons by the amount of pigment found in the pars nervosa, these distinctions are only rough and approximate. So, too, further observations concerning the structural alterations associated with various physiological and pathological conditions are required before we can completely understand the significance of such changes.

The general structure and the relationship of the different portions of the pituitary have already been described. The same combination of the parts is common to all mammals, with slight differences in regard to the extent of the pars anterior, the differentiation of the cells of the pars intermedia, the solidity or hollowness of the pars nervosa, and the relation of this nervous process to the epithelial portions. The pars nervosa always directly underlies the third ventricle, and this, as we shall see, has been held to be a matter of some importance in connexion with the pathology as well as the physiology of the pituitary. We have seen, too, that in most animals and in the human subject the anterior lobe is separated by a cleft (the original cavity of Rathke's pouch) from the posterior lobe.

Having thus got our bearings we may proceed to an examination of the different parts of the pituitary under high magnifications in order to determine the connexions of the various elements with the functions of the organ as a whole. It will be remembered that each part—the pars anterior, the pars intermedia and the pars nervosa—presents specific and distinct morphological characteristics; so it will be advisable to consider them separately, in spite of the fact that the pars anterior and the pars intermedia have a common origin.

Pars anterior—As already described, this portion of the pituitary is composed of epithelial cells arranged in a more or less branching or tubular fashion. Granular secretion may be seen in the lumen of the acini (fig. 18, p. 30) or in the blood-sinuses which are large and numerous. It is, therefore, believed that the secretion of the pars anterior is poured directly into the blood-stream or stored in the form of colloid. We have noted, too, that in adults among the higher animals the epithelial cells of the pars anterior show differential staining affinities, in consequence of which the various types have been described as being chromophil and chromophobe—they stain well or indifferently. Of the chromophil cells some are acidophil and show considerable avidity for eosin, while others are basophil and stain deeply with hæmatoxylin. The chromophobe cells are tinged very lightly with basic dyes (plate 1, facing p. 30). Many investigators have sought to place these different types of cells in regular situations in the anterior lobe; but, beyond the facts that the basophils are most numerous at the periphery and that the eosinophils surround the blood-sinuses, there seems to be little justification for such descriptions, and my own experience is that no two pituitaries in any animal or human being are alike in this respect.

There are certain important normal histological phenomena associated with physiological states, which require special consideration.

Pregnancy.—Comte[1] first, and later Erdheim and Stumme[2], noticed that in pregnancy the anterior lobe enlarges considerably.

[1] Comte, L., *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1898, xxiii, 90.

[2] Erdheim, J., and E. Stumme, *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1909, xlvi, 1.

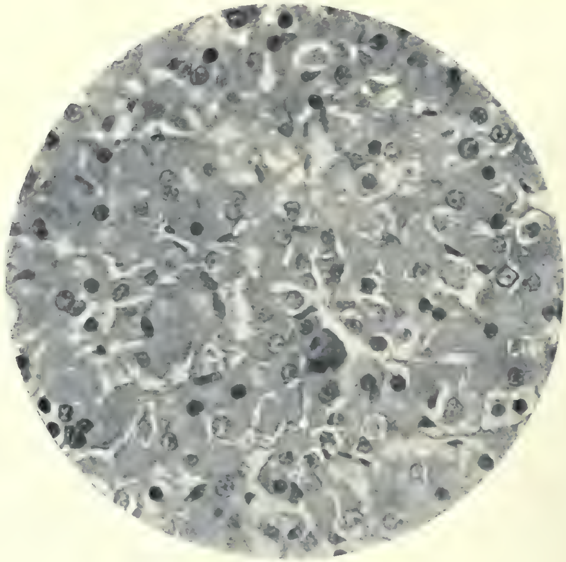

Fig. 61.

Section of the pars anterior of the pregnant rabbit, showing eosinophilia of the cells. (*Photomicrograph.*)

× 500.

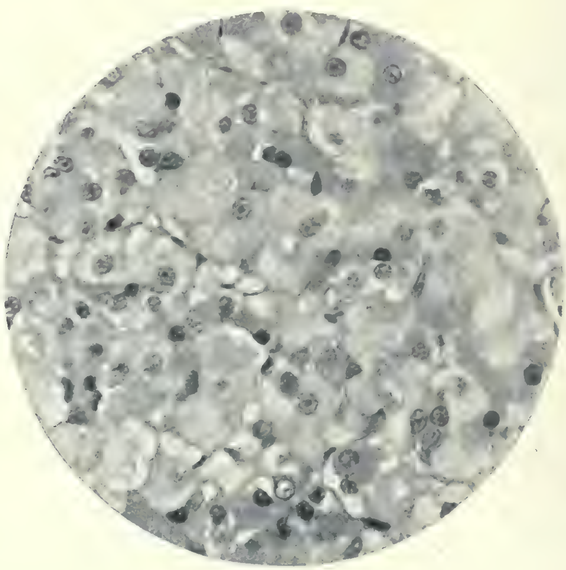

Fig. 62.

Section of the pars anterior of the pregnant rabbit, showing large chromophobe ('pregnancy') cells. (*Photomicrograph.*)

× 500.

This increase in size is stated by Erdheim and Stumme to be due entirely to changes in the chromophobe ('neutrophil', 'principal', or 'chief') cells, which now develop and become slightly more chromophil ('pregnancy cells'); that is to say, there is during pregnancy a condition of excessive activity in regard to these cells. Siguret[1] observed in rabbits a diminution in the number of the chromophobe cells and an increase in the number of eosinophil. This author also found that the change was as marked at the commencement as at the end of gestation. Lannois and Mulon[2] were the first to describe the confluence of the chromophobe cells in pregnancy, and this they designated 'syncytial'.

My own observations have impressed me with the fact that considerable variations may be found during pregnancy both in animals and women. Usually in rabbits there is, as Siguret has stated, an increase in the degree of eosinophilia—that is to say, the lightly staining eosinophil cells, which predominate in the pars anterior of this animal, stain more deeply (fig. 61). Nevertheless, I have seen extremely pronounced chromophobia in this situation during pregnancy in the rabbit (fig. 62). In women the chromophobe cells are usually plentiful in these circumstances, but this is not always the case.

The essential change, however, in the pars anterior of all animals during pregnancy is towards greater activity, and this may be represented by increased eosinophilia of the epithelial elements or by chromophobia. The chromophobe cells in these circumstances often assume a lobulated or an adenomatous arrangement (figs. 63 and 64).

Hibernation, too, produces striking changes in the histological appearances of the pituitary, and these occur in the epithelial elements of the partes anterior and intermedia—the secretory cells of this organ.

Gemelli[3] first called attention to this phenomenon, and he came to the conclusion that hibernation is a condition of pluriglandular inactivity. He found in the pars anterior that the cells are entirely undifferentiated in this physiological state.

[1] Siguret, A., *L'hypophyse pendant la gestation*, Paris, 1912.

[2] Lannois, P. E., and P. Mulon, *Compt. Rend. Soc. de Biol.*, 1903, i, 448.

[3] Gemelli, A., *Arch. p. le Sci. Med.*, 1906, xxx, 341.

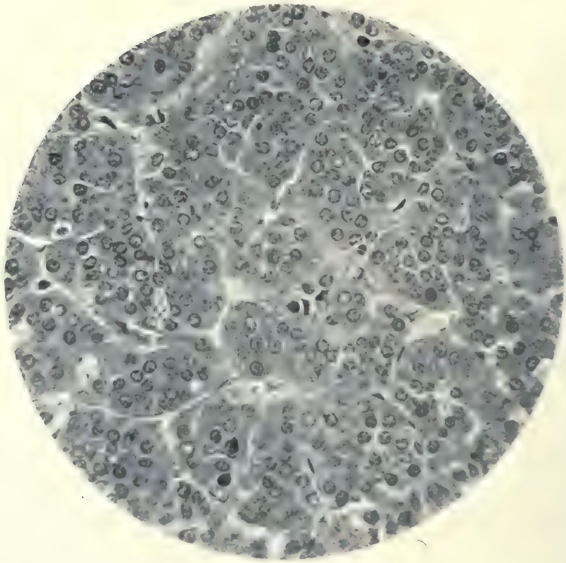

FIG. 63.

Section of the pars anterior of the pregnant guinea-pig, showing the lobulated arrangement of chromophobe cells. (*Photomicrograph.*)

× 250.

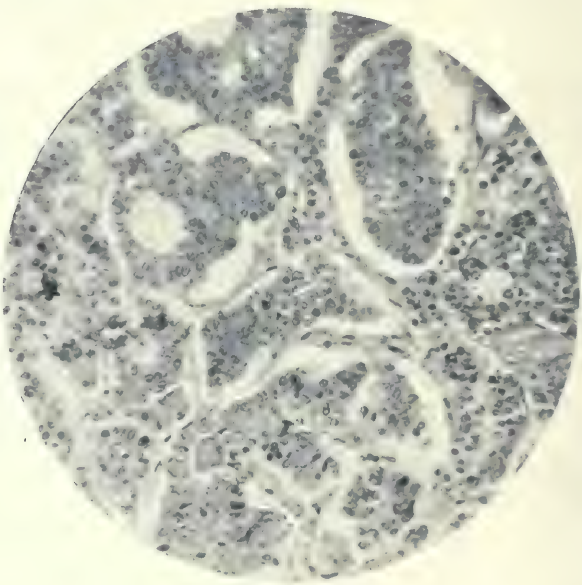

FIG. 64.

Section of the pars anterior of the pregnant woman, showing the lobulated arrangement of chromophobe cells. (*Photomicrograph.*)

× 125.

Cushing and Goetsch[1] came to a similar conclusion regarding the condition of the pituitary during hibernation. Further, these observers have suggested that physiological sleep may be associated with temporary inactivity of the pituitary. In support of this hypothesis they refer to the torpor usually seen in animals from which a large portion of the pars anterior has been removed, and to the drowsiness seen in advanced pituitary disease associated with diminished secretion—that is, in the syndrome *dystrophia adiposogenitalis*. They have called particular attention to a case of pituitary tumour in which the patient became comatose and had a low body-temperature. Cushing operated and found a cyst in the pars anterior which he evacuated. There was no general intracranial pressure. Pituitary extract made from the whole gland improved the condition, and permanent relief was obtained by the implantation of the pars anterior from a stillborn child into the subcortical tissue of the brain of the patient.

Whatever changes occur elsewhere, there is no doubt that definite alterations are found in the pituitary during hibernation. In the hedgehog and dormouse, which I have examined, during the summer the cells of the partes anterior and intermedia are active—they are swollen and blurred, and the nuclei stain faintly (fig. 65A); but during the period of winter-sleep they become shrunken and discrete, and their nuclei stain deeply (fig. 65B). Associated with these changes in the hibernating animal there is an enormous deposition of fat —just as there may be in experimentally produced or pathological insufficiency of the pituitary secretion: I have seen the subcutaneous layer of fat in the hibernating hedgehog one inch in thickness.

Brooding in hens, as already indicated (p. 53), is associated with varying degrees of pituitary insufficiency that can be recognized histologically. In the non-laying hen that is not brooding the pituitary appears less active than that of the laying hen, but more active than that of the brooding hen. The adult cock's pituitary resembles that of the laying hen. Observations concerning these physiological variations in hens do not appear to have been recorded previously. I have been unable to conduct my investigations on a large scale at the present time,

[1] Cushing, H., and E. Goetsch, *Journ. Exper. Med.*, 1915, xxii, 25.

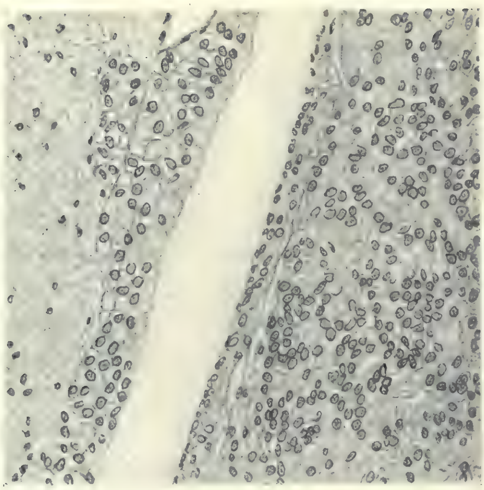

FIG. 65A.

Section of the pituitary of the normal non-hibernating hedgehog, showing the distal epithelium on the right and the juxtaneural epithelium covering the pars nervosa on the left.

× 125.

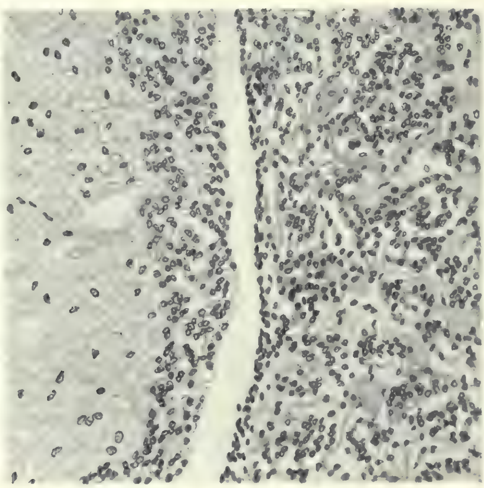

FIG. 65B.

Section of the pituitary of the hibernating hedgehog, showing the inactive shrunken cells of the distal epithelium on the right, and of the juxtaneural epithelium on the left.

× 125.

but there appeared to be no doubt whatever as to the cause and effect in the birds examined.

In the pars anterior of the laying hen there are many large eosinophil cells, mixed with chromophobe cells in an irregular manner; and the cells look blurred and swollen (fig. 66A). In the brooding hen the cells are almost all small and chromophobe; they appear shrunken and inactive, and they form definite acini, many of which contain granular secretion, enclosed in a connective tissue meshwork (fig. 66B).

The appearances of the pituitary in these physiological states —pregnancy, hibernation and brooding—throw much light on the normal physiology of the pituitary in relation to its structure; but it is improbable that this organ alone is affected in these circumstances. Gemelli's statement that hibernation is pluriglandular in origin is probably correct; and we know that all the organs of internal secretion are altered during the period of gestation, so it is probable that brooding also is associated with pluriglandular inactivity.

It is a little more difficult to deduce facts of physiological import from the comparative morphology of the pars anterior of the pituitary, and we must reserve some of the points worthy of consideration for a short discussion later of the comparative physiology of this organ. It may, however, be mentioned that among the mammals we find considerable variation in tinctorial affinities. In the ornithorhynchus all varieties of cells are found in the pars anterior, and especially we may observe several stages in the formation of the deeply staining basophil cells. In the rodents, such as the rabbit, true basophils are very rare, and in no animal below the monkey have I observed basophil colloid. This is a matter of some interest, and it probably explains the fact that eosinophilia is the most important phase of activity in these animals.

We are now in a position to consider the significance of the different types of cells found in the pars anterior. There is some divergence of opinion on this question, and two views are held: first, some authorities, of whom Gemelli[1] is the chief advocate, believe that the different types of cells have different functions; second, there are many who think with Saint-Remy[2]

[1] Gemelli, A., *Folia Neurobiol.*, 1908, ii, 167.

[2] Saint-Remy, G., *Compt. Rend. de l'Acad. des Sci.* 1892, cxiv, 770.

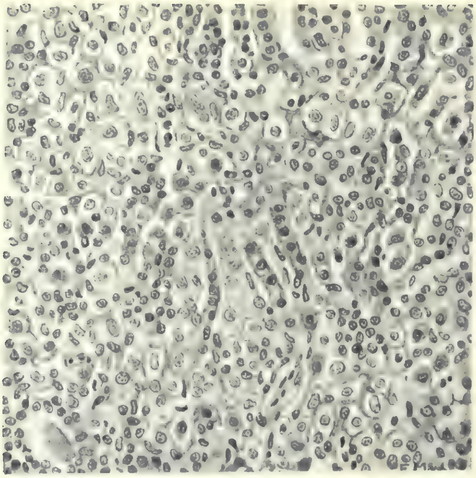

FIG. 66A.

Section of the pars anterior of the laying hen, showing large eosinophil cells mixed indiscriminately with chromophobe cells.

× 125.

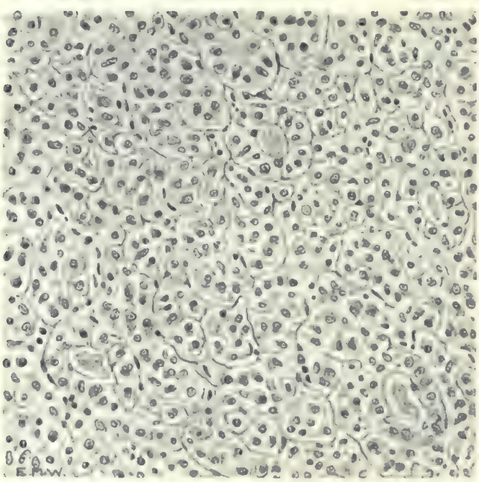

FIG. 66B.

Section of the pars anterior of the brooding hen, showing shrunken chromophobe cells divided into acinous groups by connective tissue.

× 125.

and Benda[1] that the apparently different types of cells represent the same structure in different stages of activity.

As this is a point of considerable interest and importance, as well as of doubt, I shall state my own views on the subject.

In general, my observations lead me to support the second view; and I feel able to put my conclusions into a more definite form than has hitherto been attempted.

In the first place it must be emphasized that in no part of the anterior lobe in *normal* circumstances—excluding pregnancy, brooding, and hibernation—can one find positive evidence of the presence of any one type of cell to the exclusion of the others; that is to say, at the most important points of observation all varieties are seen to be mingled together (plate 1, facing p. 30). This fact alone is significant, for it is what one would expect to find where different stages of secretory activity are in progress at the same time; and it appears to me to dispose of Erdheim's[2] argument for the opposite view, namely, that cells of the same kind may be found in clusters in *abnormal* circumstances.

With regard to the disposal of the secretion of the anterior lobe, it appears that for the most part this is carried away in the blood-channels. Thaon[3] and others have drawn attention to the fact that granular secretion may actually be seen within the blood-sinuses. Nevertheless, there can be little doubt that the secretion is chiefly taken into the blood-stream in infinitesimal quantities. In exceptional circumstances, however—influenced, no doubt, by metabolic conditions—the secretion is stored. This storage secretion, unlike the normal thyroid secretion[4], usually stains with hæmatoxylin (basophil) rather than with eosin (acidophil), although abnormally an acidophil affinity is sometimes seen. The secretion has a granular appearance when eosinophil or neutrophil, and only resembles homogeneous colloid when distinctly basophil. This basophil affinity of the formed colloid secretion gives us valuable evidence as to the

[1] Benda, C., *Berl. Klin. Woch.*, 1900, xxxvii, 1205.

[2] Erdheim, J., *Frankf. Zeitschr. f. Pathol.*, 1910, iv, 70.

[3] Thaon, P., *L'hypophyse*, Paris, 1907.

[4] It should be stated, however, that thyroid secretion may, in apparently normal circumstances, show a faintly basophil tendency.

parts played by the different cells in regard to the secretory products of the pars anterior.

In attempting to describe the secretory phases I shall consider first the eosinophil cells. These cells are the elements which produce the internal secretion of the pars anterior in normal circumstances. It is possible to observe differing degrees of staining affinity in various eventualities, and always it is the granules within the cells that stain most deeply. The eosinophil cells lie against the walls of the blood-channels, and their secretion is taken up by the blood-stream. If the secretion is not removed from these cells, chemical changes occur which alter the tinctorial affinities of the secretory products: gradually the acidophilia diminishes, and basophilia, at first slight, becomes more and more pronounced until the typical, darkly staining, basophil cell is produced.

It will be remembered that in the eosinophil cell the nucleus is central and is surrounded by an extensive cytoplasm containing eosinophil granules, and that in the deeply basophil cell the nucleus is eccentric.

Several phases may be observed in the basophils: first, they are translucent and contain granules; later, they become opaque and homogeneous, and in the transition the nucleus is gradually displaced to the periphery of the cell. Eventually, the basophil cell disgorges dark basophil colloid. This colloid is surrounded by cells most of which are small chromophobe elements with large clear nuclei and little cytoplasm—the exhausted remains, in fact, of the basophils that have extruded their colloid material (fig. 67). These chromophobe cells regenerate, and in normal circumstances become eosinophil, and pour their secretion into the blood-vessels; or they change once more into the basophil cells, and store their secretion until such time as again they extrude it in the form of colloid. In those cases in which there is an immediate and urgent demand for the secretion of the pars anterior, as in pregnancy, the small chromophobe cells, and even some of the young eosinophils, increase in size but remain chromophobe, and yield up their secretion as soon as it is formed; indeed, it is not unusual to see bubble-like collections of secretion among the cells, especially in abnormal circumstances, such as occur after removal of the thyroid.

The phases just described may be summarized in a few words:

the small chromophobe cells are exhausted cells; the eosinophil cells are the active secretory cells in normal circumstances; the basophil cells form a storage secretion; and the large chromophobe cells, which develop from the small exhausted chromophobe cells or the young eosinophils, are formed only when there is an urgent and immediate need for the secretion of the pars anterior.

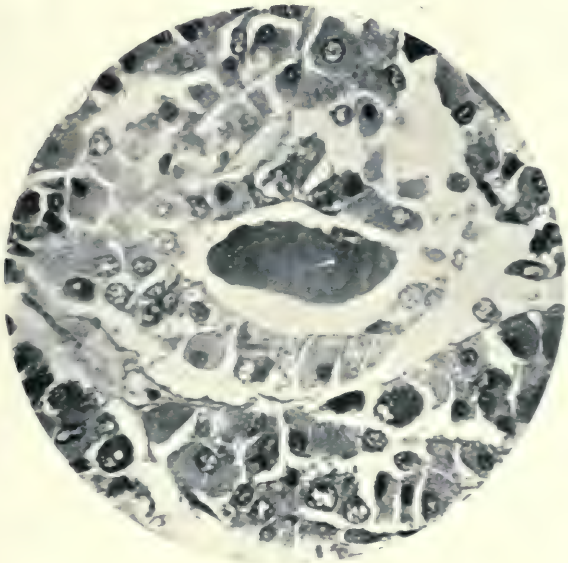

FIG. 67.

Section of the normal human pars anterior, showing basophil colloid surrounded by chromophobe cells, one or two of which are becoming eosinophil. (*Photomicrograph.*) × 500.

Thaon[1], Erdheim and Stumme[2] and others have directed attention to the lipoid particles that may be demonstrated in the epithelial elements of the pituitary. These bodies stain with sudan III, scharlack R and osmic acid. They are, of course, soluble in ether and alcohol.

My own material is not sufficient from which to draw conclusions, but there can be no doubt that the amount of lipoid material demonstrated by staining methods varies enormously in different pituitaries, and probably in different circumstances.

[1] Thaon, P., *L'hypophyse*, Paris, 1907.

[2] Erdheim, J., and E. Stumme, *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.* 1909, xlvi, 1.

In some the amount is large (fig. 68); in others there is very little. The stained lipoid bodies vary in size from dust-like particles to globular masses considerably larger than the nuclei of the cells. I have been unable to detect lipoid substances in the granular secretion found in the acini.

According to Erdheim and Stumme, chromophobe cells—including pregnancy cells—are poor in lipoids, while the chromophils—that is to say, eosinophils and basophils—may contain large quantities of these substances. But in my experience the

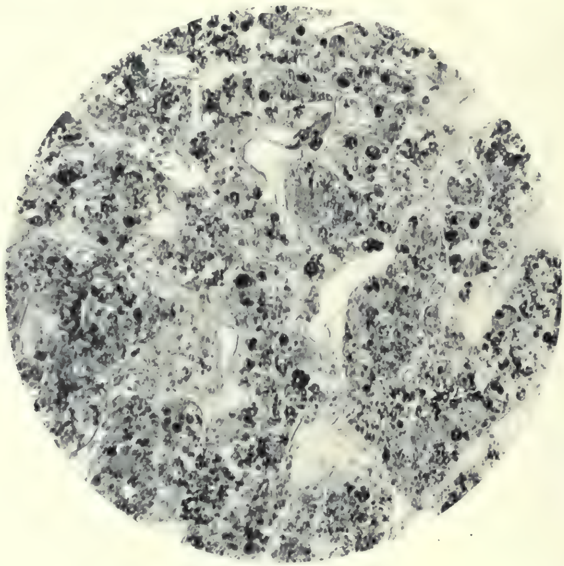

Fig. 68.

Section of the normal human pars anterior stained with osmic acid, showing lipoids in the cells. (*Photomicrograph.*)

× 125.

lipoids, as made evident by staining methods, vary in quantity, even in cells of the same character; consequently I feel that we are not in the possession of enough information to draw satisfactory conclusions as to their exact nature and import.

The fact that there are sympathetic nerves in the pars anterior is probably of significance from a functional point of view.

Pars intermedia.—As already indicated, this portion of the pituitary is derived from the pouch of Rathke and becomes

slightly differentiated from the rest of the anterior lobe with which it is continuous. For the most part it is closely attached to the pars nervosa and infundibular stalk. The pars intermedia usually invades the pars nervosa to a slight extent. We have seen that in Man and the higher mammals the invasions are superficial in normal circumstances, but that in some of the lower animals the pars nervosa is divided up by columns of cells.

It is frequently to be observed that in the part which is in relation to the stalk there are many vesicles which may contain granular secretion. This is usually neutrophil, but in conditions to be mentioned later it may be eosinophil. Sometimes the secretion appears homogeneous like colloid, and in these circumstances it is usually basophil in its staining affinity. Occasionally, secretion is found in the cleft, and is no doubt derived from the cells of the pars intermedia.

It has been shown that in different animals there are different degrees of secretory activity in the pars intermedia, so far as we can judge from the formation of obvious secretion; and that in Man there is little evidence of the production of secretion other than the colloid so frequently found above, and in, the cleft.

In abnormal conditions experimentally produced in animals a certain blurring and fusing of the cells of the pars intermedia appears to be coincidental with increased secretion.

The relationship of the pars intermedia to the production of infundibulin will be discussed directly in connexion with the functions of the pars nervosa.

Pars nervosa.—We have seen that this portion of the pituitary is chiefly composed of neuroglial cells and fibres, and that there are occasionally to be found a few ependymal cells included at the neck in those animals in which the pars nervosa is solid. When there is a central cavity, such as is seen in the cat, this is lined with ependymal cells the fibres of which run longitudinally upwards (Herring[1]). Further, we have considered the question of the nerve-supply of the pituitary, and have noted that most investigators have failed to find true nerve-fibres,

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*. 1908, i, 121.

and that it is doubtful whether sympathetics are present in this part of the pituitary.

We must now consider the histological and accessory evidence at our disposal concerning the secretion formed by the pars nervosa itself, or by the pars intermedia in conjunction with the pars nervosa. Later, we shall study the physiological properties of the extract made from these parts of the pituitary, which together form the posterior lobe and are so closely conjoined as to be inseparable on rough dissection. Whether this extract is the same as the normal secretion we need not discuss, beyond saying that it is usually believed to be so.

We have already seen that vesicles are nearly always to be found in the pars intermedia, and these contain a substance said by Biedl to resemble in appearance thyroid colloid, but in my experience it is more usual to find in animals a neutrophil granular secretion. It is most probable that this material represents the normal secretion of the pars intermedia.

Osborne and Swale Vincent[1] found that by careful dissection they could separate the central portion of the posterior lobe from the epithelial investment, and that whereas an extract of the former gave the typical effects of infundibulin, an extract made from the epithelial portion gave much less definite results. Further Osborne and Vincent[2] have shown that extracts of other nervous tissues do not possess the same physiological activity as an extract of the posterior lobe.

Herring[3] has recently confirmed the results obtained by Osborne and Vincent to the extent of finding that although both extracts stimulate muscle-contractions, the one made from the pars nervosa is from two to five times more powerful than the extract of the pars intermedia. Herring also found that an extract of pars intermedia in strengths of 0·5 per cent. and less has no specific action on the blood-pressure or renal excretion; whereas an extract of the pars nervosa in so low a strength as 0·005 per cent. produces the characteristic pressor and diuretic effects (see pp. 105 and 109).

[1] Osborne, W. A., and S. Vincent, *Brit. Med. Journ.*, 1900, i, 502.
[2] Osborne, W. A., and S. Vincent, *Journ. Physiol.*, 1899–1900, xxv, 9.
[3] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1915, viii, 245 and 267.

Miller, Lewis and Matthews[1], on the other hand, maintain that it is the cells of the pars intermedia which produce infundibulin, and that the pars nervosa is inactive in this respect. These observers also found that it was impossible to obtain pressor effects from an extract of the stalk, and they conclude that "there is, therefore, a distinct interruption in the path of secretion of the pressor substance from the pars nervosa to the ventricle". This is opposed to Herring's view concerning the passage of secretion from the pars nervosa to the third ventricle.

Evidence as to the different actions of extracts of the pars intermedia and pars nervosa must be carefully received; for, in the first place, it is practically impossible to remove all the epithelial elements from the surface of the pars nervosa, especially in the region of the stalk, and, in the second, islets of pars intermedia cells may be found in the pars nervosa. A glance at some of the illustrations in the section on comparative anatomy (p. 40 and following) will make these difficulties obvious.

Miller, Lewis and Matthews[1] obtained pressor effects from the contents of a cyst in the pars intermedia. Herring[2] was unable to obtain any definite effect from the contents of the cleft. Hamburger[3], likewise, found that the contents of the cleft were devoid of any pressor action.

Herring[4] was the first to describe what he called 'hyaline' bodies in the pars nervosa. He considers that they represent the active secretion of the cells of the pars intermedia, which is passed into the pars nervosa. Further, he believes that these bodies stream upwards towards the neck, or infundibulum, and that finally they pass into the third ventricle, and so into the cerebrospinal fluid. Herring also found that they are very much more numerous in the pars nervosa after thyroidectomy.

Cushing and Goetsch[5] subsequently investigated the question, and on the main points they agree with Herring. But these

[1] Miller, J. L., D. D. Lewis, and S. A. Matthews, *Amer. Journ. Physiol.* (*Proc. Amer. Physiol. Soc.*), 1910–1911, xxvii, xvii.

[2] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1915, viii, 245 and 267.

[3] Hamburger, W., *Amer. Journ. Physiol.*, 1904, xi, 282.

[4] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.

[5] Cushing, H., and E. Goetsch, *Amer. Journ. Physiol.*, 1910, xxvii, 60.

writers also came to the conclusion that some of the 'hyaline' bodies represent degenerated wandering cells, and that other 'hyaline' bodies consist of secretion which has escaped or has been forced from the vesicles of the pars intermedia. They state that whereas the secretion in the pars intermedia is basophil, these 'hyaline' bodies are faintly eosinophil. They also assert that they found the colloid from the vesicles physiologically inactive; but they do not state how they obtained their material. Last, these investigators found in the cerebrospinal fluid an active substance resembling infundibulin in its physiological actions. From this they conclude that it is proved beyond doubt that the active principle of the posterior lobe or pars intermedia is passed directly into the third ventricle.

Now, if this method of secretion prove to be indisputable, it represents a most remarkable train of events, and one which has no parallel in the animal economy. But, although I have myself observed all the histological details mentioned by these authors, I would hesitate to conclude that to histological features so unusual in connexion with secretory activity is to be assigned the representation of a novel method for the distribution of an internal secretion. The very fact that some so-called 'hyaline' bodies are without nuclei and others contain them indicates the true nature of these bodies (fig. 69). They are cells undergoing degeneration, which may in the process disperse their contents. Again, it must be noted that they are always very granular, and are not hyaline in structure nor do they resemble the homogeneous colloid seen in the vesicles of the pars intermedia in the sightest degree; but they do resemble exactly the granular secretion-cells and masses (fig. 53) and the granular collections in the vesicles (figs. 49 and 52) seen in the pars intermedia of cats and dogs.

On histological evidence I originally formed the opinion that the cells of the pars intermedia alone produced the pressor substance which I called 'infundibulin'[1].

The work of Miller, Lewis and Matthews[2] is directly opposed to the view of Herring, for they found that an extract of the stalk had no pressor action. They believe that the cells of the

[1] Bell, W. Blair, *Brit. Med. Journ.*, 1909, ii, 1609.

[2] Miller, J. L., D. D. Lewis, and S. A. Matthews, *Amer. Journ., Physiol.* (*Proc Amer. Physiol. Soc.*), 1910–1911, xxvii, xvii.

pars intermedia alone are concerned in the production of infundibulin.

This whole question is undoubtedly a difficult one, but I feel that the idea of a secretion actively moving towards the third ventricle is disproved by the fact that these 'bodies' must be degenerated cells, since they sometimes possess the remains of nuclei. Yet this point appears to have been noted by Herring, for he says: "Secretion goes on either by emptying of material from the cells into the lymph, or possibly by a breaking down

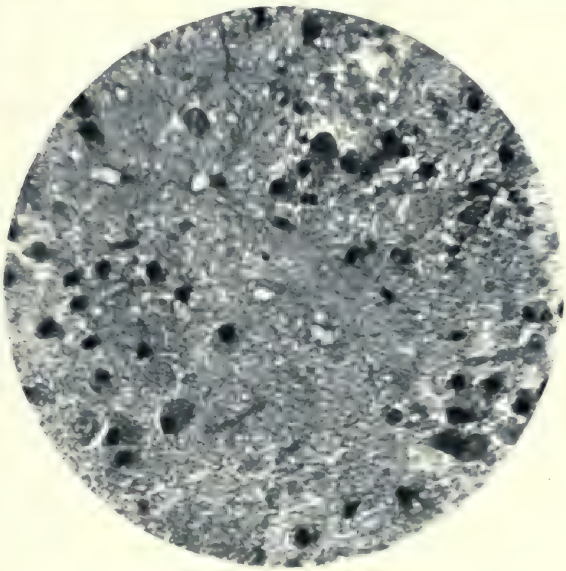

FIG. 69.

Section of the pars nervosa of the normal cat, showing granular bodies, some with nuclei, some without. (*Photomicrograph.*)

× 500.

and destruction of the whole cell. The latter, indeed, is the more probable fate of isolated epithelial cells, and seems to occur at times in the epithelial investment itself"[1].

It is, moreover, a fact of some importance that one rarely sees many of these granular bodies in normal circumstances; and after thyroidectomy I have not always seen a great increase in their number.

My present opinion is that the secretion of the pars intermedia

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.

and of the posterior lobe is taken up by the blood-stream. In support of this view attention may be called to the morphological facts that there is a network of blood-vessels beneath the pars intermedia, and that in some animals, such as the ox, the pars nervosa has a very rich internal blood-supply. At the same time I am quite aware that the cells of the pars intermedia wander into the pars nervosa, and there degenerate (fig. 69). Any secretion they contain is, no doubt, absorbed by the capillary vessels. It seems quite possible, also, that the cells of the pars intermedia both store their secretion in the form of colloid and, like the anterior lobe, pass some of it directly into the blood-stream. In order to reach the blood-vessels the secretion may pass through the pars nervosa. If this be so, as seems certain, it is possible the pars nervosa in some way alters the character of the secretion before it reaches its destination; this view[1], which I believe to be correct, whatever the final destination of the secretion may be, is supported by Herring[2].

We shall, directly, consider more fully the evidence concerning the question of the presence of infundibulin in the cerebrospinal fluid.

[1] Bell, W. Blair, *Arris and Gale Lectures*, *Lancet*, 1913, i, 937.

[2] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1914, viii, 245.

CHEMICAL EXAMINATION OF THE PITUITARY TISSUES, AND THE EVIDENCE REGARDING THE PRESENCE OF INFUNDIBULIN IN THE BODY-FLUIDS

CHEMISTRY OF THE PITUITARY

VERY little work has been carried out in regard to the chemistry of the pituitary body.

An examination of the whole gland shows that it is rich in calcium and phosphorus, but this may be on account of the nervous elements in the pars nervosa.

Schnitzler and Ewald[1] have described the existence of iodine in the anterior lobe, and concluded that it is probably in the same form as in the thyroid gland.

Halliburton, Candler and Sikes[2], and Wells[3] have failed to confirm this observation.

Biedl[4] states that the colloid in the anterior lobe is insoluble in water, alcohol and ether. This substance is unlike mucin in that it swells with acetic acid, and afterwards dissolves.

The secretion of the posterior lobe is soluble in water, and is not destroyed by boiling; consequently the active principle is not a protein. It has been found to be dialyzable, and it has certain important physiological actions that will be described later.

Suprarenin, which is probably of a quite different chemical composition, has been made synthetically, but up to the present time the actual chemical composition of infundibulin

[1] Schnitzler, J., and K. Ewald, *Wien. Klin. Woch.*, 1896, ix, 657.

[2] Halliburton, W. D., J. P. Candler, and A. W. Sikes, *Quart. Journ. Exper. Physiol.*, 1909, ii, 229.

[3] Wells, H. G., *Journ. Biol. Chem.*, 1909-1910, vii, 259.

[4] Biedl, A., *Innere Sekretion*, 2nd ed. 1913.

has not been definitely determined, although Aldrich[1] has obtained a crystalline picrate and sulphate which have a pressor action. Houssay[2], also, claims to have obtained infundibulin in a crystalline form. Recently Führer[3] has placed on the market a substance called 'hypophysin'. This is stated to contain several different substances, one of which acts on the uterus alone. It is said that Führer's preparation can be made from both the anterior and posterior lobes.

Dale[4] has produced evidence to show that infundibulin is not one of the groups of bodies to which belong suprarenin, the active principles of ergot and the pressor substance that is found in putrid meat.

The same investigator has also shown that whereas ergotin annuls the effect of suprarenin subsequently given, yet it in no way affects the action of infundibulin on arterial and uterine contractions.

Schäfer and Herring[5] believe, from their experiments, that pepsin destroys the pressor effect of infundibulin, but does not interfere with its diuretic action. They state, also, that trypsin has no effect whatever on the extract. Dale[4], however, observed exactly reverse effects in regard to the actions of pepsin and trypsin; and he gives some very convincing tracings of his results. Pepsin, he states, does not change infundibulin at all, whereas trypsin entirely destroys it in a few hours, so far as its physiological activity is concerned.

INFUNDIBULIN AND THE CEREBROSPINAL FLUID

Cushing and Goetsch[6], following the suggestion of Herring[7] concerning the passage into the cerebrospinal fluid of the so-called 'hyaline' bodies which may be seen in the pars nervosa,

[1] Aldrich, T. B., *Amer. Journ. Physiol.* (*Proc. Amer. Physiol. Soc.*), 1908, xxi, xxiii.

[2] Houssay, B. A., *Revist. Soc. Med. Argent.*, Buenos Aires, 1911, 268 (Reprint).

[3] Führer, H., *Zeitschr. f. d. Ges. Exper. Med.*, 1913, i, 397.

[4] Dale, H. H., *Biochem. Journ.*, 1909, iv, 427.

[5] Schäfer, E. A., and P. T. Herring, *Proc. Roy. Soc. Biol.*, 1906, lxxvii, Ser. B, 571.

[6] Cushing, H., and E. Goetsch, *Amer. Journ. Physiol.*, 1910, xxvii, 60.

[7] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.

endeavoured to prove that the cerebrospinal effusion contains infundibulin. Further, Weed and Cushing[1] state that injections of infundibulin increase the rate of cerebrospinal secretion. They inserted a graduated and calibrated needle into the third ventricle of the dog, with the skull and meninges intact except for a small perforation equal in size to the diameter of the needle. The drops of cerebrospinal fluid were taken as an indication of the secretory rate. These investigators, believing the formation of cerebrospinal fluid to be secretory, make the surprising statement that in response to an injection of infundibulin "a prolonged flow from the ventricle may continue even after death, and may reach an amount apparently in excess of the normal content of the ventricles". This seems an extraordinary post-mortem phenomenon, and one which requires extensive confirmation before it can be seriously considered.

Carlson and Martin[2] criticize the hypothesis of Herring and the observations of Cushing and Goetsch regarding the passage of infundibulin directly into the cerebrospinal fluid. These authors say: "It is obvious that the conclusions drawn by Cushing and Goetsch from their experiments are open to a number of grave objections. The cerebrospinal fluid used in most of the experiments was pathological, and was concentrated 20 to 25 times, and the intravenous injections were made into another species. Finally, no control experiments were reported on blood or serum from the same individuals yielding the cerebrospinal fluid".

Carlson and Martin found that the hæmodynamic action of the cerebrospinal fluid was solely due to the quantity injected, as is the case with defibrinated blood or Ringer's solution: there is, in fact, no evidence of a specific pressor or depressor effect.

These observers are careful to state, however, that their negative results do not prove that cerebrospinal fluid is free from pituitary secretion; but, as they say, we have as yet no satisfactory test for this secretion in the fluids of the body. When such tests have been worked out Carlson and Martin think that the distribution of pituitary secretion in the body-fluids will prove to be similar to that of all the other internal secretions so far

[1] Weed, L. H., and H. Cushing, *Amer. Journ. Physiol.*, 1915, xxxvi, 77.
[2] Carlson, A. J., and L. M. Martin, *Amer. Journ. Physiol.*, 1911, xxix, 64.

studied, the concentration being greatest in the blood and least in the cerebrospinal fluid. With these statements I entirely agree.

Cow[1], apparently under the impression that the cerebrospinal fluid has definitely been proved to contain infundibulin, asserts that the infundibulin content of this secretion is increased after injections of extracts of the duodenal mucous membrane, which he believes contains a hormone that excites activity in the pituitary.

[1] Cow, D., *Journ. Physiol.*, 1915, xlix, 441.

INJECTION, INGESTION AND ABSORPTION EXPERIMENTS

IMMEDIATE RESULTS OF INTRAVENOUS INJECTIONS, OF ABSORPTION OF EXTRACTS IN SOLUTION AND OF GRAFTS

PROBABLY the most important and fruitful work carried out in connexion with the pituitary has been concerned with the physiological results of injections of the extracts into the living animal: certainly these results have been the most far-reaching in their application to morbid conditions.

In this place I shall describe the physiological actions of the extracts on the different organs and systems as obtained in the laboratory, and shall merely indicate the practical application of them, for this aspect of the subject will be discussed in more detail later.

Circulatory system

In 1895 Oliver and Schäfer[1] described the action of an extract of the whole pituitary upon the blood-pressure. These observers were, at the time, investigating the physiological effects of extracts made from chief organs of internal secretion, and they also gave an account of the pressor effect of suprarenal extract—that is, of the medullary portion of this organ. They stated, however, that the suprarenal extract is more powerful in this respect than that made from the pituitary. As the result of these observations and statements, the suprarenal product obtained clinical recognition, while the physiologically active principle of the pituitary remained in obscurity.

[1] Oliver, G., and E. A. Schäfer, *Journ. Physiol.*, 1895, xviii, 277.

In 1898 Howell[1] made some further observations.

First, he found it is the extract of the posterior lobe alone—that is, of the pars nervosa and the pars intermedia, which come away together when the pituitary body is divided at the cleft—that has the pressor action. In this respect he found the extract of the anterior lobe to be inactive—an observation subsequently confirmed by many other investigators.

Second, he observed that the cardiac rhythm is considerably retarded, and that the heart-beat is increased in force by the injection of an extract of this portion of the pituitary (fig. 70). This effect is believed by Dale[2] to be partly due to a direct action on the heart-muscle, and partly to a retardation of the flow in the coronary vessels.

Third, Howell noticed that second and subsequent injections of infundibulin, if given soon after the first, produce little or no effect until the first has all been destroyed or excreted by the organism.

In the following year Hedbom[3] found that the rate of beating in the isolated mammalian heart is considerably decreased on perfusion with infundibulin in Ringer's solution. Cleghorn[4] in the same year obtained results similar to those described by Hedbom.

Also in 1899, Schäfer and Swale Vincent[5] verified these experiments on the heart, and showed, further, that the slowing of the pulse is not constant—an observation I have myself confirmed in regard to the human subject—but that when present the effect is not abolished by atropine or by section of the vagi. These observations prove, therefore, that the action of the extract is peripheral in its effect.

Schäfer and Vincent noticed, too, that a fall in the blood-pressure follows the second and subsequent doses, if they be given soon after the first. Osborne and Vincent[6] subsequently found that this effect is produced by the depressor substance found in most organic extracts. It is certain, moreover, that it

[1] Howell, W. H., *Journ. Exper. Med.*, 1898, iii, 245.
[2] Dale, H. H., *Biochem. Journ.*, 1909, iv, 427.
[3] Hedbom, K., *Skand. Arch. f. Physiol.*, 1899, viii, 147.
[4] Cleghorn, A., *Amer. Journ. Physiol.*, 1899, ii, 273.
[5] Schäfer, E. A., and S. Vincent, *Journ. Physiol.*, 1899, xxv, 87.
[6] Osborne, W. A., and S. Vincent, *Brit. Med. Journ.*, 1900, i, 502.

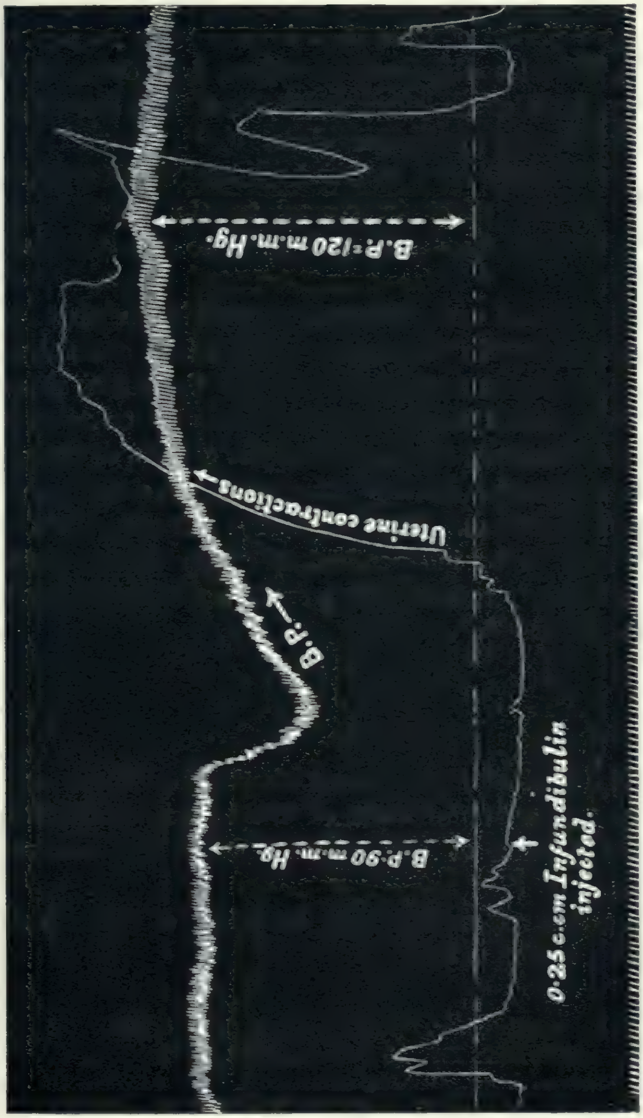

Fig. 70.

Kymograph-tracing showing the pressor effect of an intravenous injection infundibulin on the blood-pressure and uterine contractions of a pregnant cat. It will be observed that there is a preliminary fall in the arterial tension, and that the heart-beat is slower, but increased in force, after the injection.

is usual to see a preliminary fall of blood-pressure before the rise occurs (fig. 70).

Mummery and Symes[1], and Hick and I[2] independently observed that the blood-pressure is maintained at a high level for a much longer period of time than is seen after an injection of suprarenin. We also observed, as others had done, that a second dose has little or no effect until some time has elapsed since the administration of the first dose.

We shall see directly that it has been stated that infundibulin has a specific effect in regard to the renal vessels, but this point is best discussed in regard to the production of diuresis.

Dale[3] and de Bonis and Susanna[4] have shown that contraction is produced in the pulmonary arteries and arterioles by infundibulin. This is interesting in view of the facts, demonstrated by Brodie and Dixon[5], that the muscular coats of the smaller arteries of the lung are not under the control of the sympathetic nervous system, and that suprarenin does not produce vaso-constriction in them. The coronary arteries, also, are thought by some[6,7] to be independent of sympathetic control; but, like the pulmonary arteries, they are affected by the pressor action of infundibulin[3,4,8].

Spleen

Magnus and Schäfer[9] have shown that infundibulin causes contractions in the muscular coat of the spleen, producing a decrease in the volume of the organ. Dale[3] has confirmed this observation.

We shall see that advantage may be taken of this effect in certain affections of the spleen.

[1] Mummery, P. L., and L. Symes, *Brit. Med. Journ.*, 1908, ii, 786.
[2] Bell, W. Blair, and P. Hick, *Brit. Med. Journ.*, 1909, i, 777.
[3] Dale, H. H., *Biochem. Journ.*, 1909, iv, 427.
[4] Bonis, de V., and W. Susanna, *Zentralbl. für Physiol.*, 1909, xxiii, 169.
[5] Brodie, T. G., and W. E. Dixon, *Journ. Physiol.*, 1904, xxx, 479.
[6] Schäfer, (quoted by Dale[3]) *Arch. de Sci. Biol. de St. Petersburg*, 1904, 251.
[7] Elliott, T. R., *Journ. Physiol.*, 1905, xxxii, 401.
[8] Pal, J., *Zentralbl. für Physiol.*, 1909, xxiii, 253.
[9] Magnus, R., and E. A. Schäfer, *Journ. Physiol.*, 1901–1902, xxvii, 9.

Respiratory system

Mummery and Symes[1] observed that a diminution in the amplitude of the respiratory movements is produced by an injection of infundibulin—an effect that may have some connexion with the action of infundibulin on the pulmonary circulation, already described. This is a matter of clinical importance.

Urinary system

Kidneys.—In 1901 Magnus and Schäfer[2] published experiments to show that the extract of the posterior lobe produces diuresis. Further, they stated that whereas all the other arteries in the body are constricted by the active principle of the extract, the arteries of the kidney are dilated, and that there is an increase in the kidney-volume. Subsequently, Schäfer and Herring[3] found that diuresis occurred even when the arteries in the kidney failed to dilate, and when the general vasoconstriction was absent after repeated doses of the extract; consequently they came to the conclusion that there must be direct stimulation of the secretory cells of the kidney during the excretion of a specific active principle.

Herring[4] has recently stated that it is only an extract from the pars nervosa that produces diuresis and an increase in the kidney-volume. An extract made from the pars intermedia, like that of the pars anterior, is inactive in this respect.

The view of Schäfer and Herring that there is stimulation of the secretory cells of the kidney by the extract of the pars nervosa has found support in the experiments of Dale[5], who has observed that infundibulin is excreted in the urine. Further, Dale does not believe that there are two active principles, but, rather, that there is one which has both a pressor and a diuretic effect.

Cushing[6] believes that the pars posterior contains both glycogenolytic and diuretic substances.

[1] Mummery, P. L., and L. Symes, *Brit. Med. Journ.*, 1908, ii, 786.

[2] Magnus, R., and E. A. Schäfer, *Journ. Physiol.*, 1901–1902, xxvii, 9.

[3] Schäfer, E. A., and P. T. Herring, *Proc. Roy. Soc. Biol.*, 1906, lxxvii, Ser. B, 571.

[4] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1915, viii, 245 and 267.

[5] Dale, H. H., *Bio-chem. Journ.*, 1909, iv, 427.

[6] Cushing, H., *Boston Med. and Surg. Journ.*, 1913, clxviii, 901.

Cow[1] has recently endeavoured to prove that the pituitary is activated in regard to its diuretic function by a hormone from the gastrointestinal tract which is absorbed along with ingested fluids. Hashimoto[2] had previously stated that the diuretic effect of extracts of the duodenal mucous membrane is entirely due to their saline contents. Cow, however, disputes this point of view, and adduces arguments in favour of the specificity of duodenal extract in the respect mentioned.

Bladder.—Frankl-Hochwart and Fröhlich[3] first described the effect of infundibulin on the bladder. They state that strong contractions are always produced.

Dale and Laidlaw[4] were unable to obtain the same result, and in our earlier experiments[5] we did not observe any definite action on the vesical musculature. Subsequently, I found that in the presence of considerable distension—such as could be produced by the use of the cannula and manometer apparatus, to be described presently in connexion with the recording of uterine contractions—expulsive contractions can usually be produced by the intravenous administration of infundibulin (fig. 71).

I found, too, that, after the bladder had apparently been emptied with a catheter and only an occasional drop of urine was following, an intravenous injection of infundibulin caused the immediate evacuation of the residual urine in a series of rapid drops, and that shortly after the bladder had been completely emptied a further rapid outflow of drops occurred (fig. 72). The second flow probably represented increased secretion from the kidneys—that is, a diuretic effect.

We shall see later that in clinical practice infundibulin is very unreliable in regard to the evacuation of the bladder.

[1] Cow, D., *Journ. Physiol.*, 1915, xlix, 441.

[2] Hashimoto, M., *Arch. f. Exper. Pathol. u. Pharkamol.*, 1914, lxxvi, 367.

[3] Frankl-Hochwart, L. von, and A. Fröhlich, *Arch. f. Exper. Pathol. u. Pharmakol.*, 1910, lxiii, 347.

[4] Dale, H. H., and P. P. Laidlaw, *Journ. Pharmacol. and Exper. Therap.*, 1912, iv, 75.

[5] Bell, W. Blair, and P. Hick, *Brit. Med. Journ.*, 1909, i, 777.

Uterus

In 1907 we were engaged in investigating uterine contractions in the rabbit[1]. Extracts of all the ductless glands were employed, and among them an extract of the posterior lobe of the pituitary obtained from the ox.

We found that although the resting—that is, the non-pregnant and non-œstrous—uterus in the rabbit did not react, the menstruating and pregnant uterus contracted very violently in pithed animals, when an intravenous injection was given. We noticed, also, that the range of action was considerably longer and more powerful than was the case when suprarenin had been injected.

Before this date Dale[2] had illustrated incidentally the effect of an extract of the pars posterior upon the uterus, but the illustration with no comment in the text was buried in a paper on the action of ergot, and was quite unknown. It is possible that other laboratory workers may have used infundibulin for comparative tests.

In a later paper Dale[3] criticized the negative results obtained on the resting uterus of the rabbit, and he stated that the resting uterus of the cat will always react to the extract. It must be remembered, however, that the resting uterus of the rabbit undergoes marked seasonal changes, in the winter especially, when there is a considerable degree of atrophy.

Dale made the valuable observation that whereas the effect of suprarenin on the uterus is negatived by a previous injection of ergotine, the action of infundibulin is not affected in the same way.

In estimating the degree of contraction we employed a new method whereby a special cannula (fig. 73) full of saline solution was passed up the vagina, and, under guidance through a small incision in the abdominal wall, into a uterine horn in which it was tied with a woollen ligature. The cannula was then connected with a manometer containing saline solution and attached to an air-bellows with a recorder. By this means we obtained

[1] Bell, W. Blair, and P. Hick, *Brit. Med. Journ.*, 1909, i, 777.

[2] Dale, H. H., *Journ. Physiol.*, 1906, xxxiv, 163.

[3] Dale, H. H., *Biochem. Journ.*, 1909, iv, 427.

a record of the total expulsive effect. Figure 70 shows a tracing of the effect produced on the uterine contractions, as well as on the blood-pressure, by an intravenous injection of infundibulin in a pregnant cat.

Further, we found that the isolated uterus suspended in Ringer's solution contracts on the addition of infundibulin—an effect that indicates that the action of infundibulin on the uterus is peripheral.

Fig. 73.

Uterine cannula for recording the expulsive contractions of the uterus in animals.

Alimentary tract

Intestines.—During the course of our work on uterine contractions we discovered that the infundibular extract may produce a remarkable pressor effect on the intestinal muscles.

Our attention was first called to this phenomenon by the observation that on several occasions actual defecation was produced at regular intervals in a pithed rabbit. At each evacuation there was a sudden rise in the blood-pressure (fig. 74).

Records of the intestinal movements are, however, best obtained by tension-sutures attached to a piece of isolated bowel suspended in Ringer's solution, and connected with a lever. In many cases we find that on the addition of infundibulin

to the solution there is relaxation, and cessation of the normal contractions (fig. 75); but that often this is preceded by a powerful contraction (fig. 76).

Ott and Scott[1], Houssay[2] and others have confirmed these results.

Bayer and Peter[3] found that in the isolated intestine after an initial diminution in the movements there is a marked increase in their amplitude. These observers consider the first effect to be due to stimulation of the sympathetic fibres which inhibit the muscular contractions, and that the second is the result of the stimulation of the nerve-fibres connected with Auerbach's

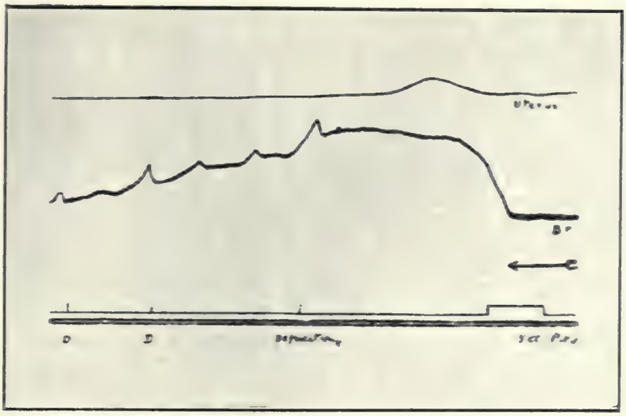

FIG. 74.

Kymograph-tracing showing rises in the elevated blood-pressure corresponding to acts of defecation (D) in the rabbit after an injection of infundibulin.

plexus. Bayer and Peter think that there are two active principles responsible for these opposite effects.

Young[4], also, has recently shown that infundibulin has a well-marked action on the intestine of the cat, raising the tone and causing the development of large oscillations; but he points out that the watery solution of the extract must be fairly strong—not less than 2 per cent.

[1] Ott, I., and J. C. Scott, *Proc. Soc. Exper. Biol. and Med.*, 1911, viii, 48.

[2] Houssay, B. A., *La Ciencia Med.*, Buenos Aires (Reprint. No date); *Revist. Soc. Med. Argent.*, Buenos Aires, 1911, 268 (Reprint).

[3] Bayer, G., and L. Peter, *Arch. f. Exper. Pathol. u. Pharmakol.*, 1911, lxiv, 204.

[4] Young, A. W., *Quart. Journ. Exper. Physiol.*, 1915, viii, 347.

Dale and Laidlaw[1] working with dogs were unable to obtain any increase in the intestinal movements.

As we shall see, there is little doubt as to the power of infundibulin to produce contractions in the atonic intestinal muscles of the human subject—a condition occasionally seen after abdominal operations.

It may be mentioned here that we have found that comparatively the greatest range of action both in regard to the blood-pressure, intestinal movements, and uterine contractions can be obtained when there is loss of tone in the muscles concerned.

Stomach.—In 1910 I recommended infundibulin for the treatment of postoperative atony and dilation of the stomach[2]. The effect obtained clinically was subsequently confirmed experimentally by Houssay[3]—the pressor effect being observed on the isolated stomach. This investigator[4] has also noted that injections of infundibulin cause an increase in the flow of gastric juice, due to stimulation of the secreting cells.

Mammary glands

In 1911 Ott and Scott[5] announced that infundibulin acts as a galactogogue on the actively secreting mammary gland. MacKenzie[6] subsequently confirmed this finding. This is an unexpected, and at present not satisfactorily explained, phenomenon. The effect is so rapid that it would seem improbable that the active principle is excreted by the mammary glands, and in its passage stimulates the secreting cells.

Hammond[7] states that the effect is not brought about by the expulsion of milk which is stored in the cells and would have been obtained at the next milking, but rather by stimulation of the mammary epithelium. Nevertheless, Hammond found only a slight increase of the daily yield of milk. Further,

[1] Dale, H. H., and P. P. Laidlaw, *Journ. Pharmacol. and Exper. Therap.*, 1912, iv, 75.

[2] Bell, W. Blair, *The Principles of Gynæcology*, 1910.

[3] Houssay, B. A., *La Ciencia Med.*, Buenos Aires (Reprint. No date).

[4] Houssay, B. A., *La Sem. Med.*, Buenos Aires, 1913 (No. 46) p. 5.

[5] Ott, I., and J. C. Scott, *Proc. Soc. Exper. Biol. and Med.*, 1911, viii, 48.

[6] MacKenzie, K., *Quart. Journ. Exper. Physiol.*, 1911, iv, 305.

[7] Hammond, J., *Quart. Journ. Exper. Physiol.*, 1913, vi, 311.

Hammond states that the quality of the milk procured by the injection of infundibulin is normal except for an increase in the percentage of fat. It was found, however, that in the subsequent milkings there was a drop in the fat-percentage, the other constituents remaining normal.

There is no evidence that the increased secretion is due to elevation of the blood-pressure, for it is said by Schäfer and MacKenzie[1] and by Hammond[2], that expulsion of milk occurs, although in lessened quantities, after repeated doses of the extract, in which circumstances the blood-pressure is not raised. Hammond, and Simpson and Hill[3] state that there is a rapid decrease in the quantity of milk to be obtained after the first increase.

I have found that if one gland, from which the nipple has been amputated, be exhausted after an intravenous injection (fig. 77), and the nipple from another mamma on the same animal be amputated fifteen minutes later, there will also be an immediate, rapid outflow of milk from this organ, as the result of the intravenous injection of infundibulin administered in the first instance (fig. 78). This is interesting in connexion with the fact[4] that an histological examination of adjacent mammary glands, one of which has been incised and emptied by the administration of infundibulin, shows that in the exhausted gland the alveoli are empty and their walls are retracted, while in the adjacent mamma the alveoli are distended with milk (fig. 79).

Hammond's and MacKenzie's experiments appear to some extent to negative the view that infundibulin acts on muscular tissue in the breasts, and thus leads to the mechanical expulsion of milk. Schäfer[4], however, in a recent paper, opposes the view that the infundibular hormone stimulates the secretory epithelium of the mammæ, and expresses the opinion that the increase in the milk obtained is due to contraction of plain muscle-fibres in the alveoli. It appears to me that all the experimental facts accord best with this view, that the increase in the rate of expulsion is due to a single pressor effect upon the muscle-fibres in the walls of the alveoli—a view held by most physiologists.

[1] Schäfer, E. A., and K. MacKenzie, *Proc. Roy. Soc. Biol.*, 1911, lxxxiv, Ser. B. 16.

[2] Hammond, J., *Quart. Journ. Exper. Physiol.*, 1913, vi, 311.

[3] Simpson, S., and R. L. Hill, *Quart. Journ. Exper. Physiol.*, 1915, viii, 377.

[4] Schäfer, E. A., *Quart. Journ. Exper. Physiol.*, 1915, viii, 379.

FIG. 77.

Kymograph-tracing showing an increased milk-drop rate in the guinea-pig after an intravenous injection of infundibulin.

FIG. 78.

Kymograph-tracing showing the rapid milk-drop rate from a second mamma fifteen minutes after the first mamma had been exhausted, as shown in Fig. 77.

Apart from the effect of infundibulin, just mentioned, on the mammæ of the lactating animal—due partly to the natural elasticity of the walls of the alveoli, and partly to the contraction of the unstriped muscle to be found therein—the epithelial cells in the alveoli may be emptied of their milk contents during the process. I have, however, been able to obtain but slight evidence that the secretion in the cells is added to that in the alveoli already distended and unable to evacuate their contents. An histological examination of the mammæ of a lactating animal removed before and after the administration

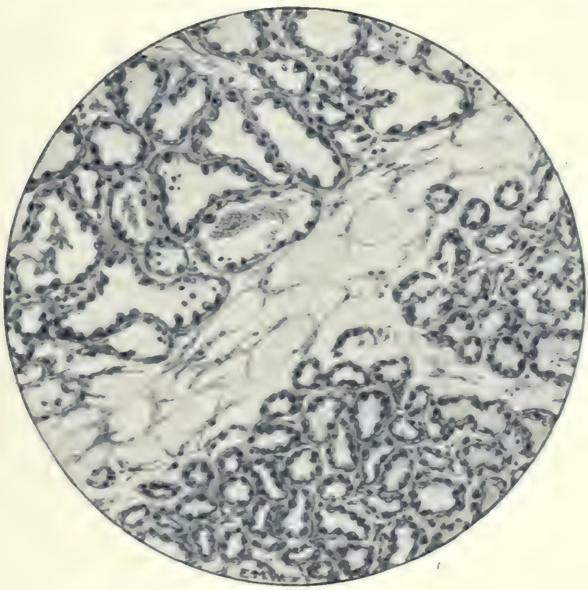

FIG. 79.

Section of the edges of adjoining mammæ in the guinea-pig, showing below alveoli emptied after an intravenous injection of infundibulin and excision of the nipple, and above the alveoli of the adjacent unemptied mamma.

× 125.

of infundibulin shows a slight difference in the size of the alveoli in the different circumstances (fig. 80).

I have, also, made experiments, hitherto unrecorded, which bear on the question of the stimulation of mammary secretion. Strictly speaking, they concern the late, rather than the immediate, action of the pituitary hormones, but I shall consider them here rather than under the next sub-heading.

I was anxious to discover whether the mammary epithelium of the virgin animal could be stimulated into any semblance of secretory activity by injections of pituitary extracts. In all cases one mamma was first removed to serve as a control to the subsequent histological examinations of the remaining mammary glands at the conclusion of the experiments.

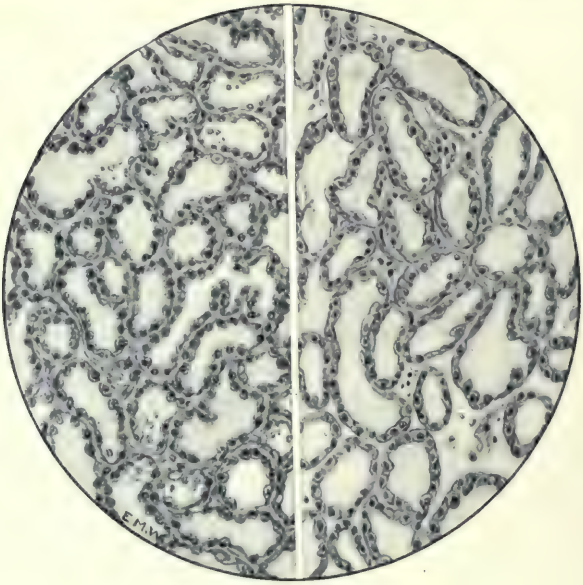

FIG. 80.

Sections of mammæ from a guinea-pig. On the left are shown the alveoli of a mamma removed for control. On the right are the alveoli of the corresponding mamma of the opposite side, from which the milk was not allowed to escape after an intravenous injection of infundibulin. It will be noticed that there is apparently a slight filling of the vesicles after the administration of infundibulin.

× 125.

1. Three adult virgin guinea-pigs received injections of a saline extract of the pars anterior. Of these two received 20 injections of 0·5 c.c. of this extract (equivalent to 0·25 gramme of fresh pars anterior substance) on alternate days; and one only 7 injections, when it died.

2. Six adult virgin guinea-pigs received injections of a saline extract of the pars posterior. Of these three received 18 injections of 0·1 c.c. (equivalent to 0·02 gramme of fresh pars posterior substance). They were all found dead on the day after the last injection, and on the same date. The

other three animals each received 27 daily injections, and remained well.

The mammæ, removed from the animals in both experiments, after they had died or had been killed, were carefully examined, but in no case was any change observed which could be construed into an indication of secretory activity.

It seems probable, therefore, that extracts of the pituitary cannot of themselves arouse activity in the breasts. At the same time, it is not possible to assert on the evidence of these experiments, which were concerned with virgin animals, that infundibulin does not affect the secretion of mammæ already lactating.

It may be stated, then, that the problem of the cause of the immediate increase in the flow of milk in a lactating animal, which is very definite, is still not completely solved.

Dilator muscles of the iris

In 1908 Cramer[1] showed that infundibulin produces dilatation of the pupil in the enucleated eye of the frog. On the other hand, Dale[2] states that no such effect can be obtained on the mammalian eye.

Pancreatic secretion

There is one more interesting study of the effects of the injections of extracts to which allusion must be made. I refer to the action of infundibulin on the secretion of the pancreas.

Pemberton and Sweet[3] have done the most important—indeed, the only important—work on this subject. These observers found that the pancreatic secretion is inhibited by injections of infundibulin. This result is produced repeatedly, even when the blood-pressure fails to rise after subsequent injections. Inhibition is also caused when the pancreas is stimulated by the normal excitant—hydrochloric acid—in the duodenum.

[1] Cramer, W., *Quart. Journ. Exper. Physiol.*, 1908, i, 189.
[2] Dale, H. H., *Biochem. Journ.*, 1909, iv, 427.
[3] Pemberton, R., and J. E. Sweet, *Arch. Int. Med.*, 1910, v, 466.

Immediate results of absorption from grafts

This has long been a recognized method of proving that certain tissues possess an internal secretion, and grafts of most of the hormonopoietic glands have been successfully implanted, and have continued physiologically active for a time. It is, of course, a method of local absorption. We have already noted the effect of infundibulin in Ringer's solution on the uterus and other involuntary muscles—a method of local absorption utilized to test the mode of action of the extract on these muscles. By the method of grafting we may obtain the normal effects of the internal secretion of the organ concerned.

From the work that has been done on this subject we know that certain conditions and circumstances greatly assist or modify the results of this procedure. Thus, it is almost an universal rule that autoplastic transplantation—that is, the removal of an organ or a portion of it from, and reimplantation into, the same individual—is far more successful in the immediate and late results than homoplastic grafting, in which the organ of one individual is transplanted into another of the same species, or of heteroplastic substitution from another species.

Halsted[1] laid down that for really successful transplantation there must be considerable insufficiency of the internal secretion in question—in other words, the whole or a large portion of the particular organ must be removed if implantations of the same structure are to be successful.

I have tested this statement in regard to the grafting of ovaries—one ovary being removed and after suitable treatment reimplanted, and the other left. It was found subsequently, at various periods, that the grafts were in an active condition in spite of the existence of one normal ovary. My investigations, therefore, do not entirely support Halsted's view. It is a most important question, for, if a successful reimplantation can be carried out—as I believe—before the *total* removal of an organ of internal secretion, a patient's life may in this way be secured from serious disturbances or from jeopardy.

Further, it is, of course, essential in all cases of grafting that the implantation should be made where there is a good blood-supply. I have never favoured the peritoneal cavity or equally

[1] Halsted, W. S., *Journ. Exper. Med.*, 1909, xi, 175.

avascular sites, because in such situations the graft is often smothered by a deposit of lymph, and perishes before vascular connexions can be established. Implantation into the kidney has been practised with considerable success in the case of the ovary; but grafts appear to do equally well when placed in muscle, a situation which, at any rate in the case of the human subject, is the safest and most convenient.

Moreover, the grafts must be thin: it is useless to attempt to implant large blocks of any organ, for the central portions undergo necrosis before the blood-supply can be established.

Last, it is hardly necessary to add that perfect asepsis is essential to success.

Very few observers seem to have studied the question of the implantation of the pituitary body. Crowe, Cushing and Homans[1], as we shall see later, were able to prolong the life of some of their dogs by previous or simultaneous implantation of the anterior lobe, but in no case was a permanent effect obtained.

Schäfer[2] failed to secure good results. He employed homoplastic and heteroplastic grafts in animals from which the pituitary had not been removed. Both of these circumstances may have militated against success, although, in spite of Halsted's dictum, I do not think the existence of a normal pituitary would do so.

Schäfer also tried the effect of grafts from the posterior lobe, and observed a temporary and moderate polyuria. As the graft disappeared so did the increase in the quantity of urine secreted. No doubt so long as any infundibular secretion remains to be extracted from the graft the effect mentioned may be observed, if the extract of the pars nervosa causes diuresis; but when all this is absorbed there will be a return to the previous state.

Allusion has already been made to Cushing's apparently successful implantation of a homoplastic graft in the human subject.

It is, however, clear that the small amount of work which has been done on implantation of the pituitary has not proved satisfactory; but it is also apparent that various necessary

[1] Crowe, S. J., H. Cushing, and J. Homans, *Bull. Johns Hopk. Hosp.*, 1910, xxi, 127.

[2] Schäfer, E. A., *Proc. Roy. Soc. Biol.*, 1909, lxxxi, Ser. B. 442.

conditions, already mentioned, have not always been carefully observed.

The subject is an important one, for in the future the success of some of the surgical procedures practised in connexion with the pituitary body may depend on satisfactory implantations.

LATE RESULTS OF INJECTION AND INGESTION

Schäfer[1] has investigated the effects of feeding with anterior lobe, and Cerletti[2] of injecting an emulsion into the peritoneal cavity.

Schäfer's experiments were not very conclusive, but they tended to show that there is more rapid increase in the weight of animals receiving an extract of the anterior lobe than of the controls. Cerletti found retardation in the growth of bones in the animals to which the extract was administered; but his control experiments have been considered unsatisfactory.

Metabolism experiments under these conditions have been carried out by various observers, but the results obtained have been most conflicting. Oswald[3] administered an extract of the whole gland by the mouth to dogs, but observed no effect on the nitrogen and phosphorus excretions. Malcolm[4] in a series of experiments came to the following conclusions. The administration of dried pars anterior causes retention of nitrogen and phosphorus. Dried pars nervosa (? posterior lobe) produces the same effect. Fresh entire gland produces an opposite effect in regard to the nitrogen. The dried partes anterior and nervosa (? posterior) both cause an increased output of calcium; but the former also brings about a large excretion of magnesium in the fæces, while the pars nervosa does not do so to the same extent. The same investigator found that the fresh gland has no influence on the calcium output when the animal is on a calcium-poor diet, but rather a tendency in the opposite direction. The excretion of magnesium, however, is increased.

[1] Schäfer, E. A., *Proc. Roy. Soc. Biol.*, 1909, lxxxi, Ser. B. 442.

[2] Cerletti, U., *Arch. Ital. d. Biol.*, 1907, xlvii, 123.

[3] Oswald, A., *Virchow's Arch.*, 1902, clxix, 444.

[4] Malcolm, J., *Journ. Physiol.*, 1904, xxx, 270.

Franchini[1] observed that there is a reduction in the calcium, magnesium, and phosphorus metabolism in animals fed with an extract of the whole gland. Wasting, intestinal ulceration and cardiac hypertrophy were also seen.

Thompson and Johnson[2] found that whole-gland pituitary extract stimulates the metabolism in the dog in an increasing degree even when the dose is not increased. This is shown in the output of nitrogen, urea and the phosphates, and also by the loss of body-weight.

Schäfer and Vincent[3] found that subcutaneous injections given over a length of time produce marked toxic effects : there is quickened respiration and increased pulse-rate, associated ultimately with paralysis beginning in the hind legs. Glycosuria and diuresis are almost constant symptoms in rabbits ; and Thaon[4] has recorded hæmaturia as a late result.

Carraro[5] observed that hepatic degeneration with necrosis of the liver-cells occurs after long continued injections of infundibulin.

Conti and Curti[6] state that the toxic symptoms following injections of pituitary extracts are ameliorated by the previous injection of thyroid extract or of an extract of the pituitary itself.

Rosalind Wulzen[7] found that the growth of a young fowl is retarded by the addition to the diet of fresh unmodified anterior lobe of ox's pituitary. This was shown in the body-weight and the diminished growth of the long bones. She also noted involution of the thymus. All these changes were more marked in males than in females. The results obtained appeared to be dependent to some extent on the dosage employed.

With regard to the renal excretions, Carlson and Martin[8], referring to the work of Borchardt[9] and of Goetsch, Cushing

[1] Franchini, G., *Berl. Klin. Woch.*, 1910, xlvii, 613, 670, and 719.

[2] Thompson, W. H., and H. M. Johnson, *Journ. Physiol.*, 1905–6, xxxiii, 189.

[3] Schäfer, E. A., and S. Vincent, *Journ. Physiol.*, 1899–1900, xxv, 87.

[4] Thaon, P., *L'hypophyse*, Paris, 1907.

[5] Carraro, A., *Arch. p. le Sci. Med.*, 1908, xxxii, 42.

[6] Conti, A., and O. Curti, *Boll. Sci. Med. di Bologna*, 1906, viii, 629.

[7] Wulzen, R., *Amer. Journ. Physiol.*, 1914, xxxiv, 127.

[8] Carlson, J., and L. M. Martin, *Amer. Journ. Physiol.*, 1911, xxix, 64.

[9] Borchardt, L., *Zeitsch. f. Klin. Med.*, 1908, lxvi, 332.

and Jacobson[1], which seemed to show that injections of the posterior lobe may cause hyperglycæmia and glycosuria, assert that cerebrospinal fluid, which according to Cushing and others contains infundibulin, has no such effect in meat-fed dogs.

Carlson and Martin also state that intravenous injections of large quantities of extracts of both lobes of the pituitary do not give rise to sugar in the urine—even though pushed until toxic symptoms, such as vomiting and purgation, appear.

Goetsch[2] has quite recently made some extensive investigations concerning the influence of feeding with pituitary extracts upon growth and sexual development; and he has come to the following conclusions.

A dried and powdered extract of the posterior lobe causes failure to gain in weight, loss of appetite, increased peristalsis with enteritis, muscular tremors and weakness of the hind limbs. The same effects are observed after the administration of excessive doses of whole-gland preparations, owing to the extract of the pars posterior contained therein.

The administration of dried and powdered pars anterior causes an increase in the rate of growth, and early sexual development in the young animal.

I myself have investigated the late effects on a few adult female animals of injections of extracts made from the pars anterior and the pars posterior; but no metabolism experiments were carried out. I obtained the following results.

Two guinea-pigs which received on alternate days 20 injections of 0·5 c.c. of an extract of the pars anterior lost a little weight: one animal weighing 300 grammes was found to weigh 270 grammes at the end of the experiment; and the other, which originally weighed 310 grammes, ultimately weighed 290 grammes. Such slight losses in weight may have been due to the general disturbance caused by the injections. A third animal, which was found dead after the seventh injection, weighed 500 grammes at the beginning of the experiment, and only 450 grammes at the end.

Three guinea-pigs which received 0·1 c.c. of infundibulin all gained in weight. One weighing 430 grammes ultimately

[1] Goetsch, E., H. Cushing, and C. Jacobson, *Bull. Johns Hopk. Hosp.*, 1911, xxii, 165.

[2] Goetsch, E., *Bull. Johns Hopk. Hosp.*, 1916, xxvii, 129.

weighed 500; another of 300 grammes increased to 330 grammes; and the weight of the third rose from 280 grammes to 300 grammes. Three other animals died on the same date after receiving 18 injections each, and in all probability they died of some intercurrent affection. These three guinea-pigs, also, had increased in weight: the first from 270 to 280 grammes; the second from 400 to 420 grammes; and the third from 220 to 240 grammes. In no case were the doses pushed to lethal quantities; but with the quantities used, which were not small in proportion to the body-weight, no other definite changes were detected in the condition of the animals, nor were obvious symptoms produced.

In one case a virgin guinea-pig was fed daily with 0·5 gramme of pars anterior for 45 days, then with 1·0 gramme for 14 days, and finally with 2·0 grammes for 50 days. This animal increased in weight from 390 grammes to 420 grammes.

In all cases complete post-mortem examinations were conducted on the animals, whether they died or were killed; and special attention was directed to the histological appearances of the reproductive organs and of the hormonopoietic glands. Only in the case of the pituitary was any definite change observed. This occurred in the two guinea-pigs that received 20 injections of an extract of the pars anterior. In both cases the pars anterior of the pituitary showed only chromophobe cells, which were arranged in acinous formation. In all the other cases, including the animal which was fed with dried anterior lobe, the pituitaries were normal in regard to the differential staining of the cells.

It is, perhaps, also worthy of mention that colloid was somewhat excessive in quantity in the thyroids of the animals which received injections of, and of the one which was fed with, extract of the pars anterior.

§ ii. PATHOPHYSIOLOGICAL INVESTIGATIONS

OPERATIONS ON THE PITUITARY

Of the two methods of eradication—destruction *in situ* and removal—the latter is preferable, for it is impossible in applying the actual cautery or caustics to limit the sphere of action, or exactly to destroy different parts of the pituitary body. Even when complete destruction is desired it cannot be said with certainty, although the pituitary may have been destroyed, that the lesion is confined to that organ.

DESTRUCTION OF THE PITUITARY

Destruction of the pituitary *in situ* has been attempted many times by means of the actual cautery, by caustics, such as chromic acid (Marienesco[1]; Vassale and Sacchi[2]; Fichera[3]), and by 'needling' (Lomonaco and Rynberg[4]; Gaglio[5]). The oral route through the basisphenoid has been the method of access usually employed in the former procedures, and occasionally the vertical route for destruction of the pituitary by needling.

A more interesting—if equally doubtful—method of destruction was that of Masay[6] who used a cytotoxin. He thought

[1] Marienesco, G., *Compt. Rend. Soc. Biol.*, 1892, xliv, 509.

[2] Vassale, G., and E. Sacchi, *Riv. Sper. di Freniat., Reggio-Emilia,* 1892, xviii, 525.

[3] Fichera, G., *Sper. Arch. di Biol.*, 1905, lix, 739.

[4] Lomonaco, D., and R. van Rynberg, *Atti Accad. dei Lincei,* 1901, x, 117, 212 and 265.

[5] Gaglio, G., *Arch. Ital. d. Biol.*, 1902, xxxviii, 117.

[6] Masay, F., *L'hypophyse,* Bruxelles, 1908.

a specific reaction was obtained as the result of his experiments, associated with histological changes in the pituitary; but as the group of symptoms produced included wasting, it can hardly be conceded that specific pituitary insufficiency was produced, for it has been almost conclusively proved that this state is associated with adiposity.

REMOVAL OF THE PITUITARY

The first experimental removals were undertaken by Victor Horsley[1]; but most of the animals died soon after operation, and very little information was obtained. Later Caselli[2], Friedmann and Maas[3], Vedova[4] and many others—too numerous to mention—attempted extirpation by various procedures and routes, but were unsuccessful in obtaining satisfactory results.

The methods of access employed were generally either the temporal route, or more commonly the oral. In the former the temporal bone was widely removed and the temporal lobe of that side raised, in order that the operator might reach the base of the brain. In the oral route the basisphenoid was perforated and the pituitary body scraped out with a spoon. Attempts have also been made to deal with the pituitary in animals by reaching it through the frontal fossa. In this method the frontal lobe is raised, much in the same way as that adopted for the temporal lobe in the lateral operation.

It is quite obvious that in animals the anterior route has incomparably less advantage than the lateral, and that the oral route through the basisphenoid—apart from creating an open door for sepsis—is somewhat of a shot in the dark, for the operator can have no possible idea of what he is actually removing. These remarks concerning the basisphenoidal route refer to experimental work, and do not apply to operations on the human subject, in whom decompression alone through the floor of the sella turcica by the nasal (not oral) route

[1] Horsley, Victor, *Lancet*, 1886, i, 5.

[2] Caselli, A., *Riv. Sper. di Freniat., Reggio-Emilia*, 1900, xxvi, 176 and 486.

[3] Friedmann, F. F., and O. Maas, *Berl. Klin. Woch.*, 1900, xxxvii, 1213.

[4] Vedova, Dalla, *Boll. Accad. Med. di Roma*, 1903, xxix, 150; idem 1904, xxx, 137.

may produce satisfactory results in certain lesions of the pituitary.

All the earlier experiments were, therefore, more or less complete failures; and it was not until the more recent work of Paulesco[1] who, with the aid of a surgical colleague, evolved the procedure known as the bitemporal method, that successful operations were accomplished, and reliable results obtained. Nevertheless, the published accounts of operations experimentally performed on the pituitary by the newer method of approach are still surprisingly few. It is probable that, apart from the investigations of Paulesco (1908), of Harvey Cushing and his colleagues (1909, 1910), and possibly also of Silbermark (1910), Biedl (1910) and Ascoli and Legnani (1912), no successful work has been carried out. Further, although Victor Horsley (1886) was certainly the first to perform extirpation experiments in this country, and probably in the world, there do not appear to have been any attempts either by surgeons or physiologists, in Great Britain—apart from later experiments[2] by the operator just mentioned—to conduct investigations on these lines until those recorded in the year 1917[3].

My experiments were concerned not only in an attempt to gain further information in regard to the experimental pathology of the pituitary, but also in testing the correctness or otherwise of the experiments of Paulesco[4], and of Cushing and his fellow-workers[4,5].

I shall first give a somewhat full account of my own work, as this has only recently been published and as so little has been done on the subject, also in the hope that my experiences may assist others to conduct fresh investigations which are urgently needed. Afterwards, I shall discuss together all the results obtained by the improved methods of technique since Paulesco entered this interesting field of investigation.

[1] Paulesco, N. C., *L'hypophyse du cerveau*, Paris, 1908.

[2] Handelsmann (no initial in original), and V. Horsley, *Brit. Med. Journ.*, 1911, ii, 1150.

[3] Bell, W. Blair, *Quart. Journ. Exper. Physiol.*, 1917, xi, 78.

[4] Reford, L. L., and H. Cushing, *Bull. Johns Hopk. Hosp.*, 1909, xx, 105.

[5] Crowe, S. J., H. Cushing, and J. Homans, *Bull. Johns Hopk. Hosp.*, 1910, xxi, 127.

Operative technique

In my experiments 27 bitches were subjected to operation, and of these two died as the result of the operative procedures, as distinct from the actual lesions produced in the pituitary. Only one of the deaths could be attributed to faulty surgical technique, and in this case the operation was abandoned owing to hæmorrhage from which the animal succumbed shortly afterwards. The other immediate death was due to an overdose of ether before the completion of the operation. Another animal died soon after total extirpation of the pituitary from some unknown cause—possibly from an overdose of the anæsthetic. All the other cases did well so far as the operative procedures were concerned.

Excluding, then, the two bitches that died before the completion of the operation, 25 cases are left for consideration (tables II–X).

Most of the animals used were from four to seven months old, but a few were a little older. The younger the dog is, the easier the operation, owing to the thinness of the skull and lesser risk of serious intracranial hæmorrhage.

Preliminary procedures.—For ten days previously to the principal operation the animal received daily 10 grains of formamine in the food, in order that the cerebrospinal fluid might be rendered antiseptic, as advised by Crowe[1].

Anæsthesia was produced with ether by the 'open' method a few days before the operation on the pituitary, and a small portion of one uterine horn together with part, or the whole, of the ovary on the same side were removed through a lateral abdominal incision for the purpose of control observations in connexion with subsequent changes in the genitalia. At the conclusion of this operation the whole of the top of the head and back of the neck was closely shaved, in order to lessen the time occupied at the second operation. In those cases in which a fatal result was anticipated—except in the case of bitch no. 19—the removal of portions of the genitalia was not practised, but the preliminary shaving was always effected.

Method of producing anæsthesia.—In view of the difficulty of working aseptically and comfortably during the operation on

[1] Crowe, S. J., *Bull. Johns Hopk. Hosp.*, 1909, xx, 102.

the pituitary in close proximity to the administrator, if the anæsthetic were given in the ordinary way, I decided to use an intratracheal method for the administration of ether. This was found to be ideal after we had overcome the initial difficulties, which caused us to lose certainly one and possibly two out of the first three animals submitted to operation. In all

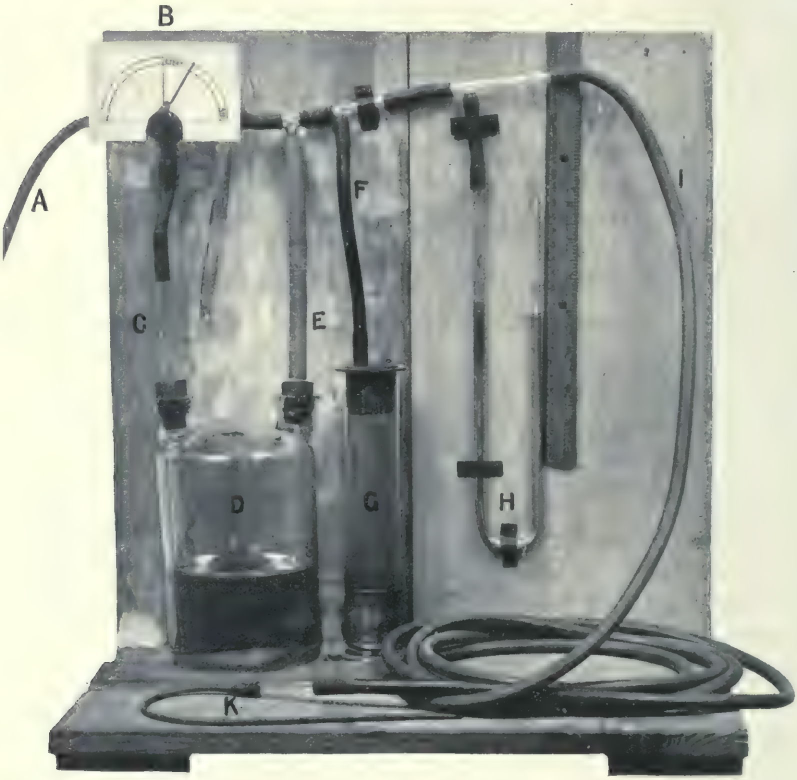

Fig. 81.

Apparatus for the administration of intratracheal ether. (*Photograph.*) A, tube from bellows; B, indicator of three-way tap; C, tube to ether-container; D, ether-container; E, tube from ether-container; F, tube to mercurial pressure-valve; G, mercurial pressure-valve; H, pressure-manometer; I, tube to catheter; K, catheter.

the subsequent cases the anæsthesia was smooth, uninterrupted and safe, and the animal was easily restored to consciousness as soon as the operation was completed by the administration of air alone through the intratracheal tube.

In figure 81 the apparatus used is illustrated. It is an easily made adaptation of the more complicated machines in

general use for the intratracheal administration of ether to the human subject. Practice may be required in passing the soft rubber catheter into the trachea. The size of the catheter is determined by the diameter of the animal's trachea, which the catheter should never fit closely. The insertion of the catheter was effected after the animal had been anæsthetized with ether by the ordinary ' open ' method.

During the intratracheal administration of the anæsthetic the animal rarely received concentrated ether-vapour : it was usually sufficient, once the animal was fully anæsthetized, to continue the anæsthesia with a mixture of air and ether-vapour, regulated by means of a three-way tap to which an indicator was attached (fig. 81, B). By this means ether, ether and air mixed, or air alone could be pumped into the lungs under uniform and limited pressure.

The anæsthetist sat at the side of the table opposite to the operator with his hand underneath the covering cloth and resting against the side of the animal, in order to judge of its condition : quiet, deep and slow respiration indicated perfect anæsthesia ; rapid, shallow breathing too deep anæsthesia ; while insufficient anæsthesia was shown by jerky and spasmodic respiration, or even by the animal coughing. The heart-beat also gave an indication of the condition of the subject.

Surgical procedures.—The animal, completely under the influence of ether-vapour administered intratracheally, was placed on its belly on an electrically heated table with the chin resting on a V-shaped depression cut out of a solid block of wood (fig. 82). The legs were fixed to the sides of the table, and the ears were tied together across the throat by means of a silk suture passed through the tips. Next, the eyes were carefully protected with dabs while the previously shaven scalp was thoroughly purified with iodine dissolved in chloroform or spirit. The animal was then entirely covered with a sterilized sheet, in which there was a small aperture through which the operation was conducted (fig. 83). The special sliding instrument-table attached to the operating-table (fig. 82) was also completely covered with a sterilized cloth (fig. 83).

A long incision, extending backwards from the root of the nose in the mid-line over the vault of the skull as far as the occipital protuberance, was carried downwards and laterally

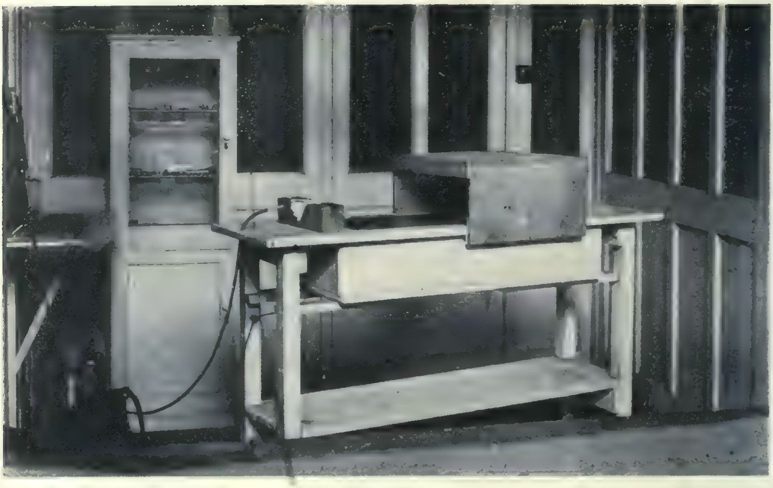

Fig. 82.

View of operating-table, showing also the sliding instrument-table, the **V**-shaped block for animal's head, and the tube leading to the ether apparatus. (*Photograph.*)

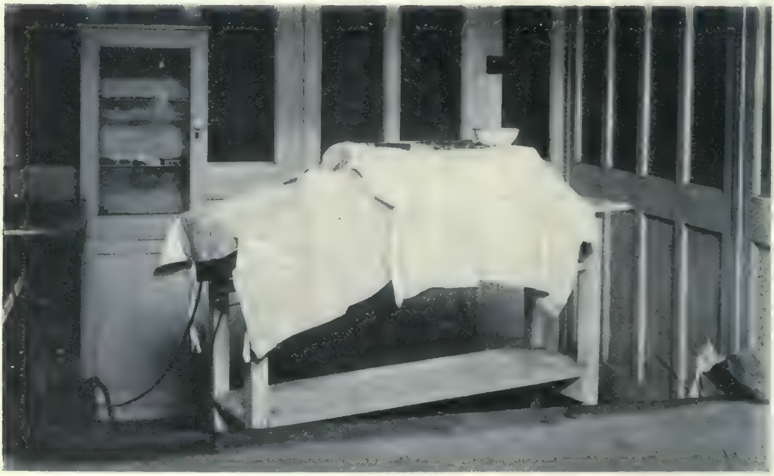

Fig. 83.

View of operating-table and sliding instrument-table covered with sterile cloths, as at the commencement of the operation. (*Photograph.*)

behind the ear on the side from which the approach to the pituitary was to be made (fig. 84). This incision was found to be better than the Y-shaped incision which was adopted by Cushing and others, and which I, also, employed in the first few operations.

Next, the skin over the right temporal region was turned

Fig. 84.

View of a bitch's head, showing the line of incision. (*Photograph.*) × ½.

down, and the temporal muscle and pericranial fascia were carefully reflected from the underlying temporal bone, which was removed widely with a trephine and rongeur. The dura mater was opened with a triradiate incision, care being taken to avoid the vessels (fig. 85). The muscle-flap was then loosely replaced together with the overlying skin, and attention was turned to the other side from which the major portion of the

operation was to be conducted: in my experiments this was always on the left side of the animal. The skin overlying the temporal region was raised on this side until the zygomatic arch was exposed. This structure was excised, together with the overlying aponeurosis, with a pair of bone-cutting forceps. The temporal muscle was reflected as on the right side, and the temporal bone widely removed with a trephine and rongeur (fig.

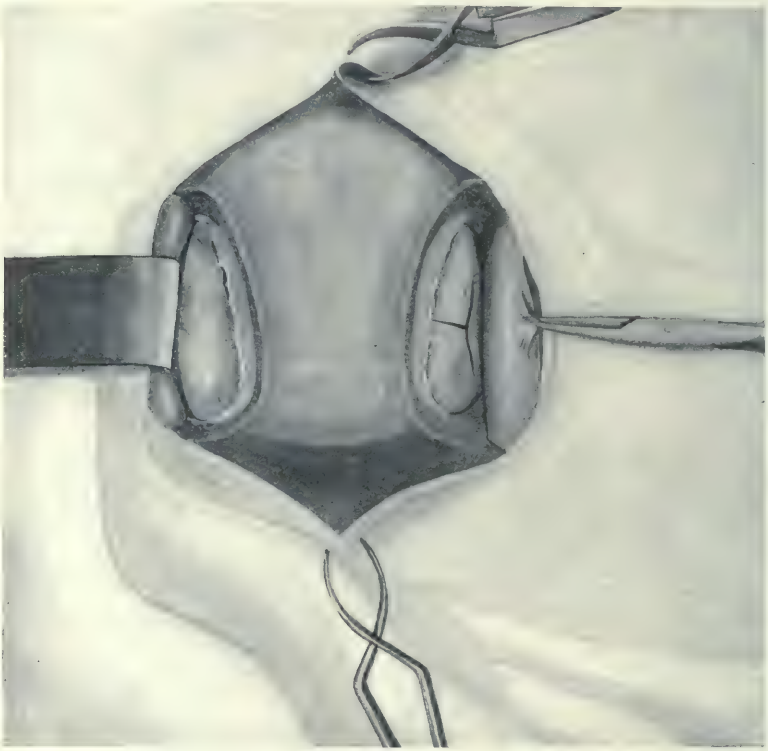

FIG. 85.

View of the field of operation at the stage when the bilateral openings have been made in the skull.

85). On this side, however, care was taken that the aperture made extended down as far as possible to the base of the skull. If there were any bleeding from the bone on either side it was readily stopped with bone-wax.

In figure 86 is seen a skiagram of the skull of one of the animals taken during life a few weeks after operation: the large aperture made on the left side is clearly shown.

FIG. 86.

Radiograph of bitch's head taken during life some weeks after operation, showing the large aperture made in the left side of the skull. (*By Thurstan Holland.*)

FIG. 87.

Soft metal spoon-shaped brain-retractor. (*Photograph.*)

× $\frac{2}{3}$.

A head-light was now required; and the next steps of the operation were conducted by the operator single-handed, for it was necessary to manage the brain-retractor with one hand, while the manipulations in connexion with the pituitary were carried out with the other. It will be evident, therefore, that as no assistant is really required for the initial and later stages, these operations can easily be performed without help; but, in order to expedite matters, such as the cutting of ligatures, an assistant is desirable.

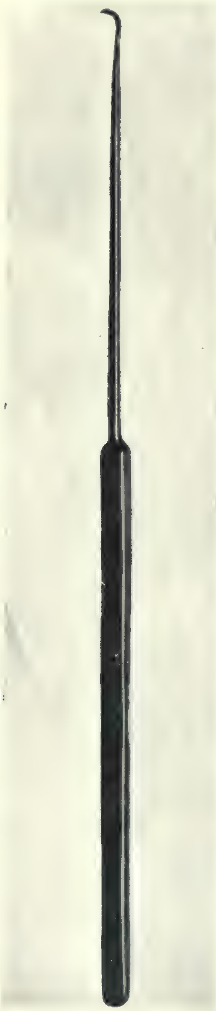

Fig. 88.

Long, hooked knife for incising the dura mater. (*Photograph.*) $\times \frac{5}{8}$.

The brain—that is, the temporal lobe on the left side—was carefully elevated with the special spoon-shaped retractor (fig. 87) recommended by Cushing. As soon as the temporal fossa had been crossed a thickened ridge of dura mater attached to the inner limit was seen. This marks the outer edge of the sella turcica, or rather the fossa to the edge of which the dura is attached, and of which the sella turcica is the most dependent part. The long, hooked knife (fig. 88) was then taken, and a slit made in the dura mater above the lower attachment just mentioned. Care was taken to carry the incision forwards rather than backwards in order to avoid wounding a large vessel frequently encountered in the dura mater. When the tip of the retractor was passed through the opening thus made, a white glistening ridge or strand of reinforced dura was disclosed, and, when the beak was tilted upwards, the third nerve passing from behind forwards and above downwards was brought into view, and in front of this the carotid artery. Between these two structures, but further in, the pituitary body was exposed (fig. 89). This organ was easily recognized by its typical apricot-like colour, which is due to the extreme vascularity of the anterior lobe. All blood and

cerebrospinal fluid was now mopped out with small dabs of wool held in forceps bent at an angle (fig. 90). As soon as the field was dry the rest of the operation planned was carried out.

Most of my operations consisted in the removal of portions of the pituitary. I used for this purpose a special pair of aural

FIG. 89.

View of the field of operation at the stage when the pituitary is first exposed. The circle of light from the head-lamp is seen in the centre of the field.

forceps (fig. 91), which I found very convenient. It was impossible to obtain, or have made, an instrument with spoon-beaks which were large enough to contain the pituitary body and which at the same time could be opened widely. With the instrument mentioned I was able to remove in several fragments most of the anterior lobe, and practically the whole of the posterior lobe intact. To remove the entire pituitary I

FIG. 90.

Angular forceps for holding wool dabs with which the cerebrospinal fluid and blood are mopped. (*Photograph.*)

$\times \frac{2}{3}$.

FIG. 91.

Aural forceps for removing portions of the pituitary. (*Photograph.*)

$\times \frac{1}{2}$.

FIG. 92.

Author's chisel-hook for cutting through the stalk of the pituitary. (*Photograph.*)

$\times \frac{1}{2}$.

had a special instrument made: this consists of a lower blade terminating in a blunt hook in which the stalk of the pituitary is caught; the upper blade, which is formed like a chisel but is blunt, can be pushed in, so as to cut through the stalk caught in the hook (fig. 92). The lower attachments of the pituitary were always first separated with a fine blunt Watson-Cheyne's dissector (fig. 93), before the stalk was cut through; after this the pituitary could be lifted out with a pair of bent forceps. This freeing of the lower attachments of the pituitary was found advisable in all operations except those in which the stalk was separated or clamped, or in which an artificial tumour was introduced.

The operation was completed by the sewing of the temporal muscles in place and the closure of the incision through the skin.

Alarming hæmorrhage sometimes occurred during the operation, especially in the older animals, but in all except one case this was controlled without difficulty; and probably there was a little carelessness in the case that was lost, for we had been accustomed easily to check the hæmorrhage with plugs of wool, and had come to regard it as of small consequence. Nevertheless, the operation was found to be much less formidable than the previous descriptions of it led us to expect. The average time occupied by the actual operations was 39 minutes.

Fig. 93.

Watson-Cheyne's dissector. (*Photograph.*) $\times \frac{1}{2}$.

The final determination of the character of the operation in the extirpation experiments was made in every case by a careful comparison of the tissue removed at operation with the post-mortem histological findings.

As it seems hardly worth while reduplicating the illustrations which show more or less identical results, only those have

been reproduced which illustrate most clearly the findings that may be considered typical and important.

Postoperative symptoms.—In no case were there severe complications, such as serious sepsis and paralyses, as the result of the operative procedures; but sometimes there was an escape of cerebrospinal fluid from the wound. Generally, the animals drank milk within a few hours of the operation, and seemed little affected the next day, when they ate meat, and were able to get out of their beds and walk about.

Of the general symptoms following operations on the pituitary, polyuria and glycosuria are not infrequent[1]—except after immediately lethal procedures when there may be anuria—and these phenomena are probably due to the action of glycogenetic and diuretic substances liberated from the pars posterior.

With respect to the cachexia said by Cushing to be specific in connexion with certain pituitary lesions, I have been unable to verify his conclusions, and I am of the opinion that the supposed typical posture attributed to the so-called 'cachexia hypophyseopriva' (see fig. 112, p. 173) is merely an attitude of weakness, which is always seen in dogs in an advanced stage of emaciation and debility from any cause whatsoever.

I shall discuss later the curious somnolence which may overtake the animals after some of these operations.

Control experiments

These were two in number, and in both cases the bitches were submitted to the same general procedures as those adopted in the other experiments, even to the previous removal of a portion of the uterus and ovary. The pituitary body was exposed at the second operation, but no part of it was removed; instead, small pieces of tissue were excised from the base of the brain in the neighbourhood. Neither of these animals showed any symptom until shortly before death, when one of them died with convulsions. This animal was probably poisoned, for another bitch which was chained up next to her died with convulsions at the same time. In both cases death occurred many months after operation, and in neither was any causal lesion found in the brain.

[1] Cushing, H., *Boston Med. and Surg. Journ.*, 1913, clxviii, 901.

In table II are given the details of these control experiments. One of the bitches (no. 9) before and 152 days after operation is shown in figures 94A and 94B. There was no change in the animal except some increase in size corresponding with the increase in age.

TABLE II.—CONTROL EXPERIMENTS.

Case.	Approximate age.	Date of operation.	Microscopical investigation of tissues removed at operation.	Killed or died.	Interval between operation and death.	Clinical symptoms.	P.M. findings.	
							Macroscopical.	Microscopical.
6[1]	9 mos.	Mar. 31	Sections show small piece of brain	Died Sept. 13	166 days	None until last 48 hrs. of life, when fits occurred	Nothing abnormal	Pituitary normal
9	9½ ,,	Apr. 28	Sections show small piece of brain	Killed Sept. 27	152 ,,	None	Nothing abnormal	Pituitary normal

Total extirpation of the pituitary

This operation (figs. 95 and 96) was effectually performed on six animals. In all cases a few cells of the reticulated portion of the pars intermedia must necessarily be left at the base of the brain, otherwise the third ventricle will be opened and part of the brain removed.

The first animal died shortly after the completion of the operation—so soon that it is possible that death was due to an overdose of ether which was used too freely during the experiment. Of the other five all died within a short time—that is to say, within periods ranging between 22 and 36 hours. In all these five cases the animals recovered from the anæsthetic, and were able to take nourishment freely. Before long, however,

[1] This animal and bitch no. 2 were kept side by side in the animal house. Both died with convulsions within a few hours of one another many months after operation. Strychnine poisoning was suspected, but the examination of the stomach of this bitch gave a negative result. No lesions were found in the brains of these animals that would account for the convulsions.

Fig. 94a.

Bitch 9 before control operation. (*Photograph.*)

Fig. 94b.

Bitch 9, 152 days after control operation. (*Photograph.*)

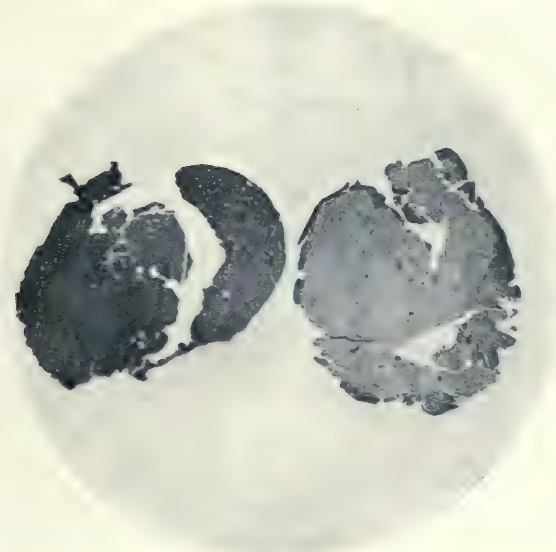

FIG. 95.

The anterior and posterior lobes of the pituitary removed at operation from bitch 1. (*Photomicrograph.*)

× 15.

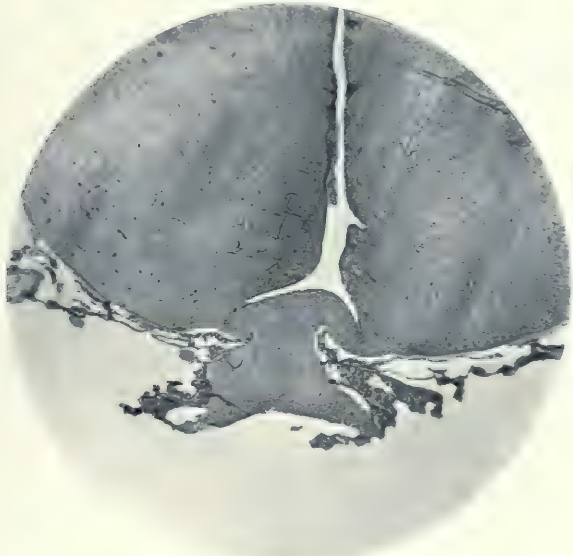

FIG. 96.

The base of the brain at the site of removal of the pituitary from bitch 1. (*Photomicrograph.*)

× 15.

TABLE III.—TOTAL, OR ALMOST TOTAL, REMOVAL OF THE PITUITARY.

Case.	Approximate age.	Date of operation.	Microscopical investigation of tissues removed at operation.	Killed or died.	Interval between operation and death.	Clinical symptoms.	P.M. findings.		Cause of death.
							Macroscopical.	Microscopical.	
1	9 mos.	Feb. 17	Sections show total anterior and posterior lobes	Died Feb. 17	Died a short while after operation	Did not recover consciousness	No hæmorrhage; small blood-clot only	Stalk with a few pars intermedia cells attached	? Anæsthetic
7	7 mos.	Apr. 7	Sections show total anterior and posterior lobes	Died Apr. 8	24 hrs.	Dullness and refusal of food; finally coma. Respirations 10. Pulse 140	Small blood-clot in sella turcica	Stalk with a few pars intermedia cells and blood-clot attached	Removal of pituitary
23	7 mos.	Sept. 8	Sections show total anterior and posterior lobes	Died Sept. 9	22 ,,	Coma. Respirations 13	Small blood-clot in track of operation	Nothing but small blood-clot the size of pituitary	Removal of pituitary
27	3 mos.	Sept. 30	Sections show total anterior and posterior lobes	Died Oct. 2	36 ,,	Dullness; then coma	Small blood-clot in sella turcica	A few pars intermedia cells with cysts below 3rd ventricle, and a small blood-clot	Removal of pituitary
29	$3\frac{1}{2}$ mos.	Nov. 9	Sections show total anterior and posterior lobes	Died Nov. 11	36 ,,	Dullness and refusal of food; finally coma	Small blood-clot in sella turcica	A few degenerated pars intermedia cells lying in blood-clot below 3rd ventricle	Removal of pituitary
30	4 mos.	Nov. 10	Sections show posterior lobe only	Died Nov. 12	36 ,,	Coma	Small blood-clot in sella turcica	A few pars intermedia cells along base of brain. No sign of anterior or posterior lobe	Removal of pituitary

they became somnolent, and, although it was sometimes possible to rouse them from this condition and to get them to stand and take food, they quickly became somnolent again as soon as they were left alone. After a few hours the respirations became very slow and coma set in; finally death supervened. The details of these operations are shown in table III.

No observable changes occurred in the genitalia in the few hours of life subsequent to operation, nor were any definite changes found in the other hormonopoietic organs in these circumstances. I anticipated finding hyperplasia in the thyroid, for Cushing is very definite on this point, but in no case was any change to be discovered.

Partial removal of the pituitary

Removal of the Anterior Lobe.—(*a*) *Total removal of the pars anterior.*—In only two experiments was the anterior lobe

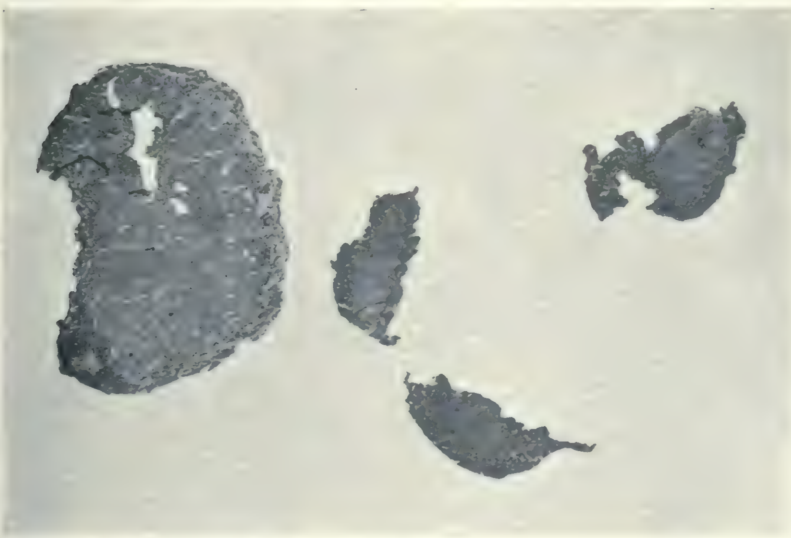

Fig. 97.

Section showing large portions of the pars anterior removed at operation from bitch 5. (*Photomicrograph.*)

× 15.

almost completely removed (table IV). It seems practically impossible to remove the entire anterior lobe without damaging

the posterior. In figure 97 are shown the portions of the pars anterior removed at operation from bitch no. 5.

In both cases death followed the extensive removal of the pars anterior within a few hours.

Nothing abnormal was observed in the other hormonopoietic organs after operation.

TABLE IV.—TOTAL OR ALMOST TOTAL REMOVAL OF THE ANTERIOR LOBE.

Case.	Approximate age.	Date of operation.	Microscopical investigation of tissues removed at operation.	Killed or died.	Interval between operation and death.	Clinical symptoms.	P.M. findings.		Cause of death.
							Macroscopical.	Microscopical.	
5	7 mos.	Apr. 6	Sections show total anterior lobe	Died Apr. 9	70 hrs.	April 7, none. April 8, none. April 9, extreme drowsiness ; finally coma	Nothing abnormal	Blood-clot in and around infundibulum. As far as can be seen the pars anterior has been removed entirely	Removal of anterior lobe
8	$5\frac{1}{2}$ mos.	Apr. 9	Sections show two large pieces of anterior lobe	Died Apr. 11	32 ,,	Dullness and refusal of food ; then coma	Nothing abnormal	No pars anterior to be found. Poor section of region	Removal of anterior lobe

The genitalia, too, showed no changes in the short period of time that elapsed between the operation and the death of the animals.

(*b*) *Partial removal of the pars anterior.*—It has been mentioned that complete removal of the pars anterior alone is practically impossible, and that the removal of nearly all of it is usually fatal. Nevertheless, it is quite easy safely to remove large (figs. 98 and 100) or small portions of the anterior lobe ; consequently observations of the effects produced by these operations should be reliable.

In table V are shown the results of removals of the pars anterior. There were five experiments, and in all the animals survived. It will be noticed that the results are not completely harmonious in regard to the details.

TABLE V.—PARTIAL REMOVAL OF THE ANTERIOR LOBE.

Case.	Approximate age.	Date of operation.	Microscopical investigation of tissues removed at operation.	Killed or died.	Interval between operation and death.	Clinical symptoms.	Weight before operation.	Weight when killed.	P.M. findings. Macroscopical.	P.M. findings. Microscopical.
							grm.	grm.		
3	4 mos.	Mar. 10	Sections show large portion of anterior lobe	Killed Oct. 6	210 days	March 11, none. March 12, drowsy. March 13, very drowsy. March 14, improved. Recovered	6680	5200	Uterus, ovaries and mammae atrophied. Thyroid small	Partial removal of pars anterior
13	?	May 4	Sections show fairly large piece of anterior lobe	Killed July 3	60 ,,	Drank some milk 1 hour after operation. No symptoms. Recovered	...	...	Uterus, ovaries and mammae slightly atrophied	Partial removal of pars anterior
15	6 mos.	June 2	Sections show small portion of anterior lobe	Killed June 11	9 ,,	None. Recovered	...	...	Nothing abnormal. (Period too short between operation and death)	Pituitary much disturbed. Much hyperplasia of existing cells of pars anterior mixed with blood-clot
19	6 mos.	July 5	Sections show very large amount of anterior lobe	Killed Oct. 21	108 ,,	Drank some milk 1 hour after operation. July 6, drowsy. July 7, drowsy. July 8, improved. Recovered	4850	5350	Nothing abnormal; but no control of genitalia taken at a previous operation	Most of pars anterior removed. Pars posterior intact
24	$4\frac{1}{2}$ mos.	Sept. 22	Sections show very large amount of anterior lobe	Killed Nov. 1	40 ,,	Animal very weak throughout whole period	...	...	Uterus, ovaries and mammae very slightly atrophied. Thyroid very large	Most of the pars anterior removed. Pars posterior intact

In no case in this series of experiments was there any observable increase in weight. Unfortunately only two bitches were weighed before as well as after operation, and of these no. 3—shown before and 210 days after operation in figures 99A and 99B—lost weight subsequently to operation; the other (no. 19) increased in weight in accordance with its normal increase in growth. Some of the animals when recovering from the operation showed the peculiar condition of somnolence already described in connexion with total removal of the pituitary. As recovery progressed this state gradually passed off.

Fig. 98.

Section showing large portion of pars anterior removed from bitch 3. (*Photomicrograph.*)

× 15.

Changes in the hormonopoietic organs other than the gonads were not found except, possibly, in the case of the thyroid from bitch no. 24. In this animal the thyroid was observed macroscopically to be considerably enlarged, but on histological examination the organ was found to be normal.

The variability in the results would not be difficult to understand if it were only in the case of the removal of small portions of the pars anterior that no symptoms were produced, while excision of large amounts produced changes in the general

FIG. 99A.

Bitch 3, before operation. (*Photograph.*)

FIG. 99B.

Bitch 3, 210 days after removal of a large portion of pars anterior. (*Photograph.*)

condition of the animal, in the genitalia and in the other hormonopoietic organs. But these were not the results that were obtained ; and it is difficult to understand why the removal of large portions (fig. 100) from one animal—no. 19—should give rise to no ill effects, while the removal of smaller pieces, as in some of the other animals, should cause definite changes in the genitalia.

In three out of the five cases in which portions of the pars anterior were removed the uterus (figs. **101A** and **101B**) and ovaries

Fig. 100.

Section showing large amount of pars anterior removed from bitch 19. (*Photomicrograph.*)

× 15.

were definitely atrophied. In these circumstances we find in regard to the uterus that there is first of all atrophy in the muscular coats, and that this is soon followed by atrophy in the endometrium. The changes in the ovaries will be described later (p. 195).

In two cases nothing abnormal was noted, but in one of these the length of time—nine days—that had elapsed between the operation and the post-mortem examination was probably not sufficient to permit atrophic changes to take place in the genitalia. In the remaining case no control was taken before

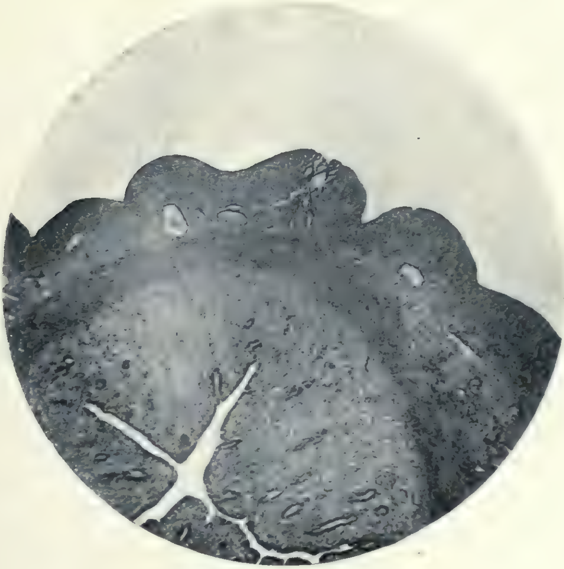

FIG. 101A.

Section of the uterus of bitch 3 before operation. (*Photomicrograph.*) × 40.

FIG. 101B.

Section of the uterus of bitch 3, 210 days after partial removal of pars anterior. (*Photomicrograph.*)

× 40.

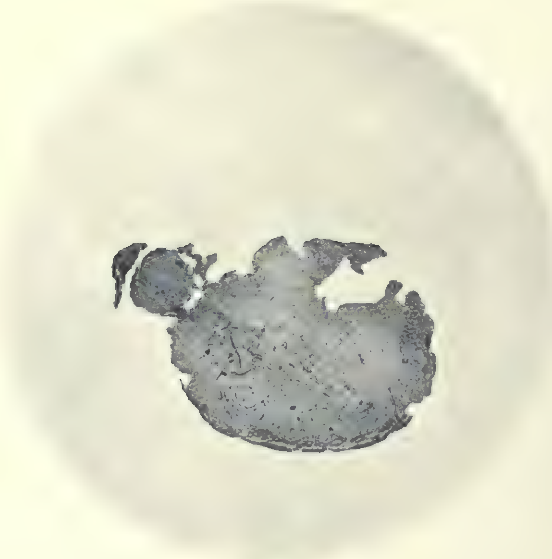

FIG. 102.

Section showing posterior lobe removed at operation from bitch 16. (*Photomicrograph.*)

× 15.

FIG. 103.

Section showing the site of the pituitary after removal of the pars posterior from bitch 16. It will be seen that a small portion of the pars nervosa at the neck was left behind. (*Photomicrograph.*)

× 15.

the operation on the pituitary, as it was intended that a fatal quantity should be removed. This, however, was not effected at the operation, although a large amount was excised (fig. 100). The uterus and ovaries showed no change from the normal after an interval of 108 days. Naturally, in any case, a considerable lapse of time must occur subsequently to the operation if definite changes in the genitalia are to be expected.

Removal of the Posterior Lobe.—(*a*) *Total removal of the pars posterior.*—In only one case was total removal of the posterior lobe effected (figs. 102 and 103). The details of this case are shown in table VI.

TABLE VI.—TOTAL REMOVAL OF THE POSTERIOR LOBE.

Case.	Approximate age.	Date of operation.	Microscopical investigation of tissue removed at operation.	Killed or died.	Interval between operation and death.	Clinical symptoms.	Weight before operation.	Weight when killed.	P.M. findings.	
									Macroscopical.	Microscopical.
16	7 mos.	June 1	Sections show total posterior lobe	Killed Oct. 7	128 days	None	grm. 4700	grm. 5100	Nothing abnormal. The uterus, mammae, and ovaries had developed since the operation	Shows absence of the pars posterior, except the neck

The animal (no. 16)—shown before and after operation in figures 104A and 104B—had no symptoms whatever. There was some increase in weight, but only in accordance with the growth of the animal. The uterus (figs. 105, A and B) and ovaries (see fig. 132, p. 198) continued to develop, and no changes were observed in the other hormonopoietic organs.

(*b*) *Partial removal of the pars posterior.*—Of this experiment, also, there was only one case. The bitch died 199 days after operation with convulsions (table VII, p. 156). It has already been suggested that the animal may have been poisoned, for this and a control animal, mentioned above, both died within a few hours of one another with the same symptoms.

So far as could be discovered no changes in the genitalia or elsewhere had been caused by this operation.

FIG. 104A.

Bitch 16 before operation. (*Photograph.*)

FIG. 104B.

Bitch 16, 128 days after removal of the pars posterior. (*Photograph.*)

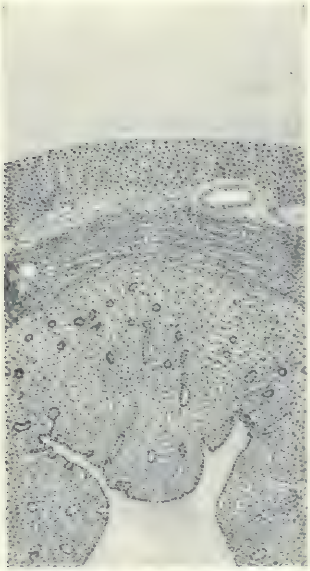

Fig. 105a.

Section of the uterus of bitch 16 before operation

× 60.

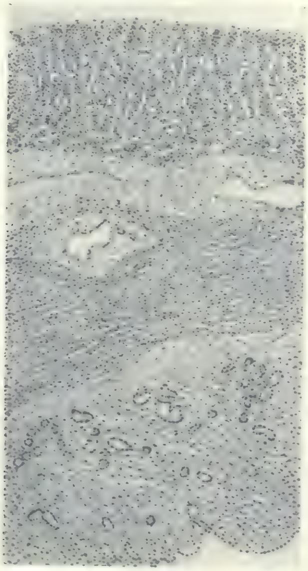

Fig. 105b.

Section of the uterus, which has developed, of bitch 16 128 days after total removal of the pars posterior.

× 60.

TABLE VII.—PARTIAL REMOVAL OF THE POSTERIOR LOBE.

Case.	Approximate age.	Date of operation.	Microscopical investigation of tissue removed at operation.	Killed or died.	Interval between operation and death.	Clinical symptoms.	Weight before operation.	Weight when killed.	P.M. findings.	
									Macroscopical.	Microscopical.
2	7 mos.	Feb. 24	Sections show small amount of posterior lobe	Died Sept. 11[1]	199 days	None until last 48 hrs. of life, when fits occurred which ultimately caused death	grm. 10,000	grm. 11,200 on Apr. 16	Nothing abnormal	Dog died on a Saturday night, and had been dead some time before post-mortem could be made. Impossible to cut good section of the parts

TABLE VIII.—PARTIAL REMOVAL OF THE ANTERIOR AND POSTERIOR LOBES.

Case.	Approximate age.	Date of operation.	Microscopical investigation of tissues removed at operation.	Killed or died.	Interval between operation and death.	Clinical symptoms.	Weight before operation.	Weight when killed.	P.M. findings.	
									Macroscopical.	Microscopical.
17	6 mos.	June 25	Sections show almost total posterior lobe and a small amount of anterior lobe	Killed Dec. 14	172 days	None. Animal came on heat, and had coitus without becoming pregnant	grm. 7350	grm. 8550	Rather fat	Sections show a large amount of anterior lobe and very little posterior lobe
25	5 mos.	Sept. 15	Sections show almost total posterior lobe with a medium amount of anterior lobe	Killed Nov. 5	61 ,,	None	5000 (on Oct. 1 after operation)	5500	Nothing abnormal.	Poor section of region

[1] See footnote on p. 141.

Combined Partial Anterior and Posterior Lobe Removals. —In both the cases of this experiment (table VIII) large portions of the pars posterior and small amounts of the pars anterior (fig. 106) were removed. In neither case were any symptoms or post-mortem appearances noted which could be ascribed to the operation. Both animals put on weight, bitch no. 17 becoming rather fat; this animal, moreover, came on heat and

Fig. 106.

Section showing portions of the pars posterior (on the right) and a small portion of the pars anterior (on the left) removed from bitch 17. (*Photomicrograph.*) × 15.

had coitus, but did not become pregnant. The genitalia continued to develop, and no changes were noted in the hormonopoietic organs.

The absence, then, of specific symptoms following the simultaneous removal of small portions of the pars anterior and large amounts of the pars posterior corresponds with the state of affairs obtaining after similar removals separately conducted on different animals.

Compression and Separation of the Stalk

The details of these operations are shown in table IX. The results which they produce are probably identical, although it is possible that absolute severance of the stalk may produce more sudden and lasting effects than compression.

These experiments, as I shall indicate more fully when discussing the results obtained by others, are of considerable interest, for in all three cases there was an increase in weight and in two (nos. 12 and 14) the condition of *dystrophia adiposogenitalis* was produced. By no other operation was I able to obtain this result.

In figures 107A and 107B bitch no. 14 is shown before and after operation, and in figures 108A and 108B bitch no. 12, before and after operation. In the second case, especially, an extreme condition of adiposity is to be seen: the body-weight of this animal increased 66 per cent. in 51 days. In figure 109 this bitch is shown laid open at the post-mortem examination.

The appearance of a dog with *dystrophia adiposogenitalis* is remarkable, and no photograph does justice to the extraordinary degree of adiposity which may occur. In general appearance the animal becomes strikingly seal-like: the head and limbs look too small for the body, the fur becomes erect and the breadth of the back causes it to become flattened on top. The young animal remains somatically infantile.

Both of the animals which showed considerable increase in weight also showed complete atrophy of the uterus (figs. 110A and 110B), and of the ovaries and mammæ.

Histological examination of the pituitary region shows that at the line of separation and compression there is a formation of new fibrous tissue, and that the cells of the underlying pars anterior are atrophied and widely separated (fig. 111).

In disposition the animal is lethargic after recovering from the postoperative somnolence which is pronounced: it sleeps a great deal. Moreover, when standing it has a typical appearance: the tail and ears droop, and the animal appears to be only half-awake (figs. 107B and 108B). In one case (no. 14) the thyroid was found to be very large indeed, and when examined histologically the vesicles were seen to be enormously distended with colloid (see fig. 126, p. 191).

TABLE IX.—COMPRESSION AND SEPARATION OF STALK.

Case.	Approximate age.	Date of operation.	Killed or died	Interval between operation and death.	Clinical symptoms.	Weight before operation.	Weight when killed.	P.M. findings.	
								Macroscopical.	Microscopical.
Compression of the stalk.									
14	7 mos.	May 18	Killed Sept. 24	129 days	Drank milk 1 hour after operation. Fair amount of adiposity, i.e. 20 % increase in weight in 71 days	grm. 6000	grm. 7100 (on July 28 w. = 7200)	Large amount of subcutaneous fat. Uterus, ovaries and mammae infantile. Thyroid very large	Sections show whole pituitary, but cells stain badly, are separated from one another in the pars anterior, and are shrunken (atrophied). The stalk is severed and replaced by new fibrous tissue. Thyroid vesicles distended with colloid
Separation of the stalk.									
12[1]	5½ mos.	May 19	Killed Sept. 24	128 days	For first 3 days extremely drowsy; afterwards became abnormally fat. Increase in weight, 66 % in 51 days	3000	5050 (same weight on Jul. 9)	Uterus, ovaries and mammae intensely atrophied: very large amount of subcutaneous fat	Sections show line of cleavage below patch of normal pars intermedia cells. The rest of the pituitary is embedded in fibrous tissue
21	6½ mos.	Aug. 31	Killed Nov. 19	80 ,,	Increased in weight	7400	8100	Nothing abnormal, except the mammae, which are infantile	Poor section: tissues badly fixed

[1] This specimen (fig. 109) is now in the Museum of the Royal College of Surgeons, England.

FIG. 107A.

Bitch 14 before operation. (*Photograph.*)

FIG. 107B.

Bitch 14, 129 days after compression of the infundibular stalk. (*Photograph.*)

FIG. 108A.

Bitch 12 before operation. (*Photograph.*)

FIG. 108B.

Bitch 12, 51 days after separation of the infundibular stalk. (*Photograph.*)

Fig. 109.

Bitch 12 laid open at the post-mortem, 128 days after separation of the infundibular stalk. The enormous deposits of fat can be well seen, also the two horns of the atrophied uterus. (*Photograph.*)

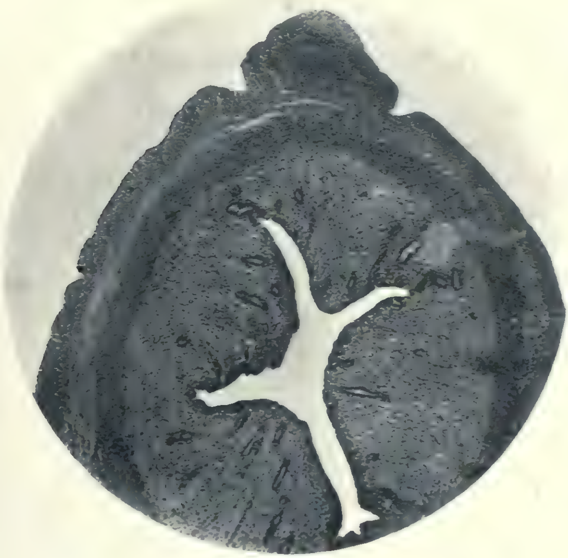

FIG. 110A.

Section of the uterus of bitch 12 before operation. (*Photomicrograph.*)

× 40.

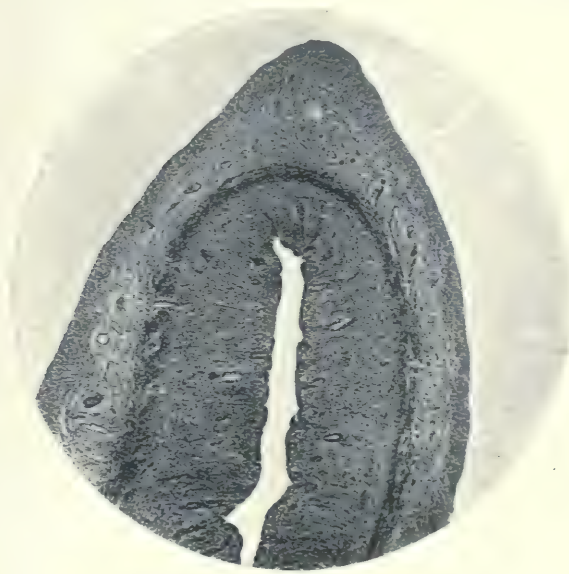

FIG. 110B.

Section of the uterus of bitch 12, 128 days after separation of the infundibular stalk. (*Photomicrograph.*)

× 40.

DISCUSSION OF RESULTS OF EXTIRPATION OF THE PITUITARY AND OF SEPARATION AND COMPRESSION OF THE STALK

It will now be of interest to see how far the foregoing experiments confirm or contradict the work of others. In this connexion it will be sufficient to consider the pioneer work of Paulesco[1], and the subsequent experiments of Cushing and his colleagues[2,3] and of Biedl[4] and his associates.

The work of Aschner[5] is less reliable, for although this investigator was able to produce certain of the abnormal

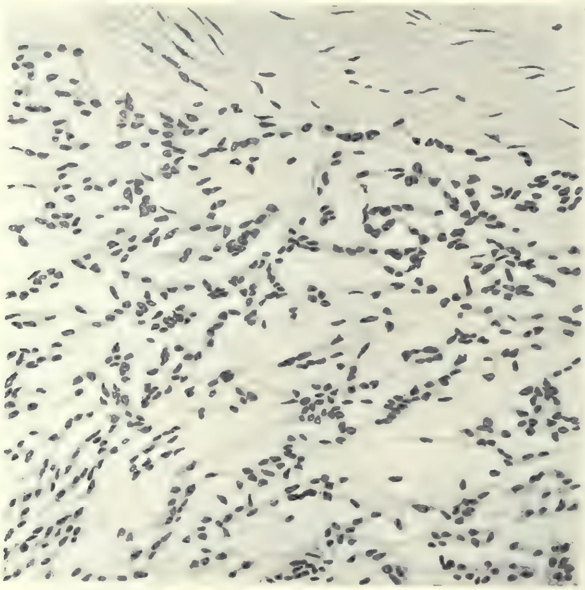

FIG. 111.

Section of the pars anterior of bitch 14 after compression of the stalk. The cells are atrophied, and new fibrous tissue is seen above, at the site of compression. × 200.

phenomena that previously had been recognized by others, his methods, which have been justly criticized by Biedl, were not exact, since he used the oral route. Ascoli and Legnani[6], also,

[1] Paulesco, N. C., *l'Hypophyse du cerveau*, Paris, 1908.

[2] Reford, L. L., and H. Cushing, *Bull. Johns Hopk. Hosp.*, 1909, xx, p. 105.

[3] Crowe, S. J., H. Cushing, and J. Homans, *Bull. Johns Hopk. Hosp.*, 1910, xxi, 127.

[4] Biedl, A., *Innere Sekretion*, 2nd ed., 1913.

[5] Aschner, B., *Wien. Klin. Woch.*, 1910, xxxii, 572.

[6] Ascoli, G., and T. Legnani, *Munch. Med. Woch.*, 1912, lix, 518.

so far as I can gather, do not appear to have clearly recognized that different lesions produce different results.

Paulesco's work, on the other hand, is of the highest merit, for by introducing the bitemporal route he at once placed the experimental possibilities on a sound basis. The results which he obtained may be summarized as follows :—

1. Complete extirpation of the pituitary caused death in a short time.
2. Partial removal of the pars anterior caused no symptoms other than adiposity.
3. Extensive or complete destruction (thermocautery) of the pars anterior resulted in death.
4. Removal of the pars posterior caused no symptoms.
5. Separation of the stalk resulted in the death of the animal.
6. Separation of the pituitary from its bed in the sella turcica produced no symptoms.

Cushing and his fellow-workers, as the result of two series of careful experiments, in which they adopted with slight improvements the technique introduced by Paulesco, obtained results very similar to his ; indeed, the only differences noted were in regard to partial removal of the pars anterior and to separation of the stalk.

Cushing and his colleagues found that separation of the stalk produced the same effects as total removal with immediate transplantation. They also believed that the adiposity which occurred in their animals after partial removal of the pars anterior was specific ; that is to say, while Paulesco had observed that the animals might become fat, Cushing and his associates were the first to recognize the importance of this adiposity, and to note that it was identical with the pathological condition previously known as *dystrophia adiposogenitalis*, since there was also genital atrophy. Further, these investigators found that in young animals persistent infantilism occurred after partial removal of the pars anterior[1].

Cushing also made the important observation that the subnormal temperature always found with *dystrophia adiposo-*

[1] Aschner also claims to have obtained *dystrophia adiposogenitalis* by partial removal of the pituitary by the oral route. There appears to be no doubt, however. that Cushing made the first communication on the subject.

genitalis can be raised by injections of an extract made from the pars anterior. This he called the 'thermic reaction'. On the other hand, according to the same investigator[1], the low blood-pressure and carbohydrate-tolerance associated with this syndrome are relieved by injections of infundibulin.

Again, Cushing and his fellow-workers found that although total extirpation was a fatal operation the effect was not so rapid in young as in older dogs.

Last, Cushing described a condition of '*cachexia hypophyseo-priva*' which was considered specific of deprivation (complete or almost complete) of secretion of the pars anterior.

Biedl[2], without giving details, states that he has confirmed all Cushing's findings, except in regard to stalk-separation, which operation, in agreement with Paulesco, he found to cause death. It is hardly worth while to dwell on Biedl's results in the absence of details other than those given in his book.

Silbermark[3], in the reference given by Biedl, with whom he was associated, discusses only the technique of the operation. Apparently the results he obtained with Biedl are recorded, without details, only in Biedl's work.

My experiments have not entirely confirmed the work of Cushing and his colleagues, which seems to be the most satisfactory of all the experimental work hitherto carried out on the subject. It will, therefore, be of interest to discuss the points of confirmation and contradiction, and to find, if possible, some explanation of the differences.

The results of my experiments concerning the effects of total extirpation of the pituitary and of the removal of very large portions of the pars anterior confirm the statements of Paulesco and Cushing that such procedures are fatal.

Sweet and Allen[4] alone of recent investigators deny that the pituitary is essential to life; but undoubtedly their technique is open to criticism.

My experiments also confirm the fact demonstrated by Paulesco and Cushing that the removal of the pars posterior produces no symptoms. Further, I have been able by means of the control

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[2] Biedl, A., *Innere Sekretion*, 2nd ed., 1913.

[3] Silbermark, M., *Wien. Klin. Woch.*, 1910, xxiii, 467.

[4] Sweet, J. E., and A. R. Allen, *Ann. Surg.*, 1913, lvii, 485.

specimens, removed before the operation on the pituitary, to show that the genitalia not only do not undergo atrophy but continue to develop in the young female after removal of this portion of the pituitary.

With regard to the points wherein my experiments gave results different from those obtained by Paulesco, Cushing and others, undoubtedly the most striking is in connexion with the production of *dystrophia adiposogenitalis*. Whereas Cushing—and probably Paulesco, although he failed to recognize the importance of the condition—found that partial removal of the pars anterior was the lesion responsible for this syndrome, in none of the cases in which I removed portions of the pars anterior did *dystrophia adiposogenitalis* supervene, although when sufficient was removed, and there was a considerable lapse of time between the operation and death, genital atrophy was usually found. In one case there was an actual loss of weight in a young animal in 210 days. This animal remained stunted. In other cases the animals increased in size.

I found, however, that the syndrome *dystrophia adiposogenitalis* followed compression and separation of the infundibular stalk. In two out of three cases there was atrophy of the genitalia with considerable adiposity: in one case the increase amounted to 66 per cent. of the body-weight in 51 days.

It is not impossible to reconcile these diverse conclusions, especially if we study the difficulties Cushing encountered when he attempted to make his experimental findings conform with his clinical observations. Believing that reconciliation was not possible, he was tempted to throw over his experimental results in favour of the clinical evidence that was in conflict with them.

It will, I think, be sufficient to call attention to the chief perplexity with which Cushing was confronted. As we have seen, the results of his experimental work indicate that *dystrophia adiposogenitalis* is due to insufficiency of the anterior lobe. But in his clinical experience Cushing found, as already mentioned, that the only symptom of the syndrome *dystrophia adiposogenitalis* relieved by the extract of the anterior lobe was the subnormal temperature. While, on the other hand, the low blood-pressure, and the carbohydrate-tolerance—and, as far as I can understand from his later writings, the genital dystrophy—were mitigated by the extract of the posterior lobe. In view, then, of these clinical

observations, how was it possible to attribute this syndrome to the experimental removal of portions of the pars anterior, as Cushing himself and others had done? Cushing solved the question by rejecting his experimental conclusions.

The results I have obtained after compression and separation of the stalk appear to explain the paradoxes. Such an operation could only interfere with the blood-supply of the whole organ; and, if infundibulin do pass directly into the third ventricle, stop this source of supply.

It is, however, hardly possible that the pars posterior and its secretion have anything to do with the matter, for all recent investigators are agreed that the posterior lobe can be removed without producing any symptoms. Further, since I found it possible to remove large portions of the pars anterior and the entire pars posterior without causing *dystrophia adiposogenitalis,* but was able to produce this syndrome by compressing and separating the stalk, it is obvious that interference with the blood-supply to the pituitary produces the condition. There seems little reason to doubt, then, that this syndrome is primarily produced by insufficiency of the pars anterior; but it appears certain that the only sure way to effect this is to interfere with the blood-supply. If this be done, we find that the cells of the pars anterior become shrunken, atrophic and discrete (fig. 111)—a state of affairs which is always found in the human subject afflicted with *dystrophia adiposogenitalis* (compare fig. 161, p. 247) and in the hibernating animal during the winter-sleep (fig. 65B, p. 88).

It is now necessary to consider how the foregoing statements can be reconciled with the facts that removal of the posterior lobe causes no symptoms, yet infundibulin relieves some of the symptoms—the lowered blood-pressure and the carbohydrate-tolerance—in *dystrophia adiposogenitalis.*

I have long held[1] that to explain these facts we must look upon the pituitary as one organ and not two. Further, from the clinical and experimental evidence of this syndrome, and from other evidence which has been discussed, it is probable that the view of Herring[2] concerning the determination of the secretion of the pars posterior solely and directly into the third ventricle cannot be sustained, and that this secretion, if required, can

[1] Bell, W. Blair, *Arris and Gale Lectures: Lancet,* 1913, i, 819.

[2] Herring, P. T., *Quart. Journ. Exper. Physiol.,* 1908, i, 121.

be, and is, taken up, like other internal secretions, by the blood-stream. It is to be remembered that the secretory cells of the posterior lobe—the cells of the pars intermedia—are derived from the same source as those of the pars anterior ; consequently while compression and separation of the stalk interrupt the blood-supply to all these cells, the ablation of the pars posterior does not remove the cells of the pars intermedia situated at the base of the brain, nor does such an operation interfere with the pars anterior. Hence it is that it becomes necessary to look upon the functions of the pituitary as a whole, and to consider this structure as one organ and not two. The fortuitous juxtaposition of the epithelial cells and the pars nervosa has probably no relation to the vital—essential and beneficial—functions with which the pituitary is concerned. Even if secretion from the pars nervosa do pass into the cerebrospinal fluid there is no evidence to show that this is essential, beneficial, or even the normal method by which infundibulin is taken up by the animal economy.

Special attention has been directed by Cushing to the peculiar somnolent condition in which the animal may exist for some time after operations which decrease the pituitary secretion, especially that of the pars anterior. This state, which has already been described, is quite characteristic. It may exist in different degrees from a deeply comatose condition to merely mental lethargy. If the animal becomes really comatose, as is the case after complete and almost complete extirpation of the pituitary, death always, in my experience, supervenes. But some animals—for example, bitch 3 in my series—become somnolent for many days and must be disturbed and lifted out of their beds in order to get them to take food. This they readily do as soon as they are sufficiently aroused. Animals that recover usually pass from this condition into one of mental apathy, which either disappears in time or persists—according to the permanence or otherwise of the diminished secretion.

There is little further to be said at present concerning the relation of experimental pituitary lesions to polyuria and glycosuria : disturbance of the pars posterior is supposed to set free glycogenolytic and diuretic substances. Cushing and his colleagues are at present engaged in investigating these questions[1], and their work is expected to modify certain existing opinions.

[1] Cushing, H., Private Communication.

EXTIRPATION COMBINED WITH IMPLANTATION OF GRAFTS

Crowe, Cushing and Homans[1] are, so far as I know, the only operators to test this method of substitution-therapy. These workers were able to prolong the life of dogs in which the total removal had been performed, but not to save them. They state that the graft remained viable for at least a month. Implantation was carried out in some cases before operation, and in others after extirpation.

In criticism of these experiments it may be said that the conditions for successful grafting (see p. 120 and following) were not strictly observed. No complete account is given by these investigators of the technique which they employed. What is described as 'previous' implantation might have been successful if a portion of the animal's own pituitary—especially of the pars anterior—had been removed at the time the graft was made, and the rest of the organ removed subsequently. Again, if a heteroplastic graft were used permanent success could not be expected. Further, the site usually chosen (cerebrum) by these workers could hardly be considered vascular enough to ensure successful implantation.

It follows, therefore, that these experiments cannot be considered very satisfactory or illuminating; indeed, it is highly probable that any benefit that occurred from the grafts, as Crowe, Cushing and Homans themselves admit, was due to the absorption of the secretion contained in the graft at the time of implantation.

STIMULATION OF THE PITUITARY IN SITU

Stimulation of the pituitary has been practised by direct and indirect methods. In the former the pituitary has been exposed—usually through the basisphenoid—and stimulated mechanically, with caustics or with electric currents. This is a very unreliable method, for it is practically impossible to limit the stimulation to the part intended, especially when electrical currents are used. In the indirect method the pituitary has

[1] Crowe, S. J., H. Cushing, and J. Homans, *Bull. Johns Hopk. Hosp.*, 1910, xxi, 127.

been excited by electric stimulation of the nerves connected with it, or by hormones injected into the circulation.

Direct stimulation.—By this means Cyon[1] observed considerable variations in the blood-pressure, and in the cardiac rhythm; and he formulated a theory which assigned to the pituitary body the function of regulating the intracranial circulation. The thyroid, he thought, took part in the same action. This hypothesis has been adversely criticized by Biedl[2] and others.

Schäfer[3], moreover, found that injury to the pituitary in dogs leads to marked diuresis, and he attributes this effect and the findings of Cyon—without supporting his general hypothesis—to an increase in the secretion which is brought about by stimulation.

Masay[4] confirmed Cyon's results, but Pirrone[5] states that stimulation of the brain in the neighbourhood of the pituitary causes vascular disturbances similar to those produced by stimulation of the pituitary itself.

Weed, Cushing and Jacobson[6] found that faradization of the pituitary causes glycosuria.

Stimulation of the pituitary by placing artificial tumours in the neighbourhood of the sella turcica is a method which I have used in an attempt to produce the symptoms of neighbourhood tumours.

The technique I adopted was to expose the pituitary by the bitemporal method already described, and after exposure to place a piece of specially prepared paste in the neighbourhood of the pituitary fossa. The paste was made of wax heated with barium sulphate to make a sterile mixture opaque to X-rays, and was placed in position while soft.

I operated in this way on three animals (table X). Two recovered quickly from the operation, and these I shall discuss

[1] Cyon, E. v., *Pflüger's Arch.*, 1898, lxxii, 635.

[2] Biedl, A., *Innere Sekretion*, 2nd ed., 1913.

[3] Schäfer, E. A., *Proc. Roy. Soc. Biol.*, 1909, lxxxi, Ser. B, 442.

[4] Masay, F., *l'Hypophyse Thèse*, Bruxelles, 1908.

[5] Pirrone, D., *Rif. Med.*, 1903, xix, 169 and 205.

[6] Weed, L. H., H. Cushing, and C. Jacobson, *Bull. Johns Hopk. Hosp.*, 1913, xxiv, 40.

directly. The third bitch was evidently in so much pain, when it recovered from the anæsthesia, owing to pressure of a very large mass of paste, that it was destroyed immediately.

TABLE X.—IMITATION TUMOUR IN SELLA TURCICA.

Case.	Approximate age.	Date of operation.	Killed or died.	Interval between operation and death.	Clinical symptoms.	Weight before operation.	Weight when killed.	P.M. findings.	
								Macroscopical.	Microscopical.
						grm.	grm.		
20	6 mos.	July 6	Killed Sept. 27	98 days	Great emaciation. Glycosuria	...	...	Large tumour at edge of sella turcica. Uterus, ovaries and mammae atrophied	Large cyst in pars anterior
22	7 mos.	Sept. 7	Killed Nov. 3	57 „	Well developed and fat. Nearly 20 % increase in 57 days	8200	9800	Tumour in front of pituitary. Nothing abnormal	The lobes are displaced in their relation to one another
26	4½ mos.	Sept. 29	Killed Sept. 29	1 hour	Seemed in pain, and therefore killed	...	...	Large tumour occupying sella turcica	

Of the other two dogs the first showed symptoms soon after operation. It became listless, and progressively and quickly lost weight, in spite of the fact that it was able to eat well from the first. Eventually the animal became extremely emaciated (fig. 112) and there was persistent glycosuria; consequently, at the end of 98 days, it was killed.

Figure 113 is a radiograph of the tumour *in situ*, taken during life.

The animal had mange, and at the post-mortem examination a small chronic abscess was found in the abdominal wall; but neither of these lesions could have been responsible for the general condition.

The tumour was found to be encapsuled and overlying the left margin of the sella turcica. The pituitary was slightly displaced, but otherwise was normal on macroscopical examination. An histological examination showed the tumour to be embedded in the overlying brain-substance and encapsuled with fibrous

tissue. The pituitary contained a large cyst in the anterior lobe (fig. 114) which appeared to be somewhat compressed.

The second of the two bitches which lived for some time after the operation, had a large artificial tumour, lying slightly further forward (fig. 115) than that in the case just described.

This animal had no glycosuria, and it increased considerably in weight during the 57 days that elapsed between the operation and the date on which it was killed.

The pituitary was found to be remarkably displaced, the pars posterior being completely detached from the pars anterior.

FIG. 112.

Bitch 20, 98 days after operation, showing the emaciation and attitude of weakness caused by glycosuria due to the pressure on the pituitary of an imitation tumour. (*Photograph.*)

On histological examination it was found that the anterior lobe was more or less in the normal position, but that the pars posterior was tilted out of the basin formed for its reception in the pars anterior (fig. 116); consequently a section through the stalk failed to show the pars anterior. In this case the displacement of the pituitary appeared to be indirect; that is to say, the floor of the third ventricle was displaced to the opposite side, and there was no actual stimulation, but rather interference with the stalk.

Such a condition would account for the increase of weight which occurred in this animal after operation. In the human

FIG. 113.

Radiograph, taken during life, showing the artificial tumour in bitch 20. It will be noted that the zygoma on the left side was excised as usual during the operation. *(By Thurston Holland.)*

subject it is, of course, well known that tumours in the neighbourhood of the pituitary usually lead to the syndrome *dystrophia adiposogenitalis* by causing atrophic changes in the secretory cells.

Paulesco[1] has published a paper bearing on the experimental aspect of this subject, but I have been unable to refer to it, as it is at present unobtainable in this country.

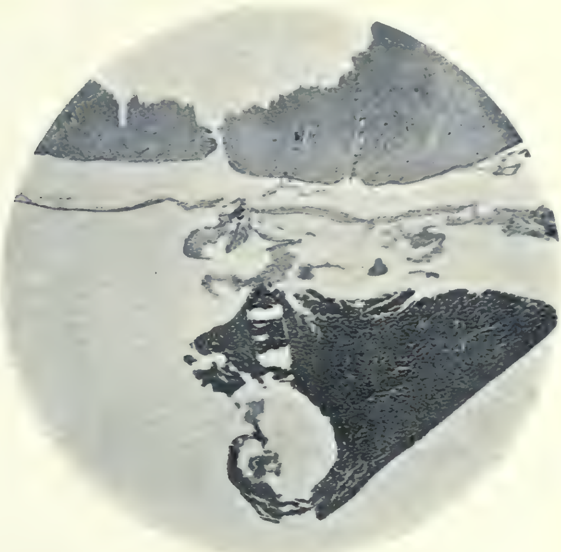

FIG. 114.

Section of the pituitary of bitch 20, 98 days after operation, showing a cyst in the pars anterior caused by an imitation tumour. (*Photomicrograph.*) × 15.

Indirect stimulation.—As already mentioned, Weed, Cushing and Jacobson[2] have shown that the pituitary may be stimulated through the main trunk of sympathetic nerve-fibres. These investigators came to the following conclusions:—

1. Stimulation of the superior cervical ganglion, by faradization or even by the manipulation necessary for its exposure, causes glycosuria in the rabbit, cat or dog.

[1] Paulesco, N. C., *Ann. de Biol.*, 1911, i, 221.

[2] Weed, L. H., H. Cushing, and C. Jacobson, *Bull. Johns Hopk. Hosp.*, 1913, xxiv, 40; *Amer. Journ. Physiol.* (*Proc. Amer. Physiol Soc.*), 1913, xxxi, xiii.

Fig. 115.

Radiograph, taken during life, showing the artificial tumours in bitch 22.
(By Thurston Holland.)

2. Stimulation of the superior cervical ganglion after exclusion of all possible downward impulses to the abdominal viscera by way of the vagi, cervical sympathetic trunks or cervical cord, leads to glycosuria. Further, a similar result follows separation of the sympathetic synapses with nicotine.

3. If the posterior lobe of the pituitary be previously removed by operation, stimulation of the cervical sympathetic fails to cause glycosuria.

These experiments support the view that the pars posterior secretes a glycogenolytic substance.

FIG. 116.

Section of the pituitary from dog 22, 57 days after operation, showing the displacement of the pars anterior and pars posterior caused by an imitation tumour. (*Photomicrograph.*)

× 15.

I have already alluded to the effect an extract of duodenal mucosa is said[1] to have on the pituitary secretion, when discussing the way in which diuresis is caused by infundibulin.

No other work with regard to the effect of injections of hormones on the pituitary has been carried out. It is a difficult field of research, but one which contains interesting possibilities.

[1] Cow, D., *Journ. Physiol.*, 1915, xlix, 441.

THE INTERRELATIONS BETWEEN THE PITUITARY AND THE OTHER HORMONOPOIETIC ORGANS

WE now come to an extremely complicated part of our subject, and one which yields results that in all probability are fraught with most illuminating meanings, had we the knowledge necessary for their complete interpretation.

As already stated, many hypotheses may be formed, and many deductions drawn from the experimental results obtained; but there are many loop-holes for the escape of the truth, which seems to be most jealously guarded in regard to the correlations of the organs of internal secretion.

In spite of the isolated positions and specific functions assigned to these organs, there can be no doubt in the mind of any one who carefully considers all the available evidence that the hormonopoietic glands are closely connected with various physiological systems, such as the vascular and genital; and that each of the various secretions augments or counteracts the others. Normally, then, the internal secretions are well co-ordinated; but lesions in any one member may interfere with the smooth-working effects of the rest. We are, however, faced with many difficulties when we seek for exact information. Thus, because we find an enlargement and apparently an increased activity in the pars anterior and pars posterior of the pituitary after removal of the thyroid, are we to suppose, as has been done by Rogowitsch[1], Cyon[2] and others, that the function of these parts of the pituitary is supplementary to that of the thyroid? If so, what are we to think of the effect of ovarian removal which produces very similar changes in the pituitary body? Does the secretion of the pituitary also supplement that of the genital glands?

[1] Rogowitsch, N., *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1889, iv, 453.
[2] Cyon, E. v., *Pflüger's Arch.*, 1898, lxxii, 635.

It is usually accepted that these things are so, but there is another side to the question. Can this pituitary activity subsequent to castration and thyroidectomy be an expression of an increased activity due to the removal of a restraining influence ?

It is probable, I think, that both effects are produced at the same time. First, there is the withdrawal of the specific ovarian secretion from the blood, and a deficit occurs in the organism in regard to this substance, whether its action be that of a hormone or of an individually active secretion. Second, the absence or limitation of the particular secretion may remove a controlling factor, as evidenced by overaction on the part of some of the remaining members of the hormonopoietic system.

It is possible that the reason why physiologically active secretions of various organs, such as the ovary, the suprarenal cortex and the anterior lobe of the pituitary, have not been obtained and utilized therapeutically is because they do not produce their effects single-handed : they must either be activated by or combined with some other substance, as they are normally in the body, before they can give effect to any properties they may possess. We have direct evidence of this in the activity of implantations of the structures mentioned, as opposed to the inactivity of their extracts.

In view of what has been said above regarding the impossibility of deducing anything definite from the facts observed, until we have the further information concerning pluriglandular effects, we shall merely describe the results of our own work and that of other observers in regard to connexion between the other hormonopoietic organs and the pituitary, without attempting to analyse too closely the complete meaning of the results obtained.

Experimental methods of investigation consist in supplying a surplus of one or more internal secretions, or in putting out of action, partly or wholly, one or more members of the hormonopoietic system.

SUPPLEMENTATION WITH PITUITARY EXTRACTS

There is no reason why the effects of excessive doses of a prepared extract of one of the organs of internal secretion should not produce definite effects on the rest, but so far no investigations appear to have been carried out on these lines, except in regard to supplementation with pituitary extract.

Renon and Delille[1] performed some experiments which, they considered, proved that repeated injections of an extract of the whole pituitary produce hyperplasia in the thyroid.

In my own experiments on guinea-pigs I injected extracts made from the anterior and posterior lobes, and I fed animals on extract of the anterior lobe.

With regard to the experiments carried out with the extract of the anterior lobe, the only definite changes noted were in connexion with the anterior lobe of the pituitary, which, strangely enough, showed evidence in all cases of abnormal secretory activity. In the animals which received injections daily the cells were almost entirely chromophobe and were arranged in a well-marked lobular disposition (fig. 117); while feeding with the same extract produced more moderate activity, that is, profuse eosinophilia of the cells, to the exclusion of the other varieties.

In the thyroids of these animals the colloid was always plentiful and the vesicles thin-walled; but it is difficult to interpret this as abnormal.

In the suprarenal cortex, after feeding with extract of the anterior lobe, there appeared to be considerable vacuolation (fig. 118), but whether this was due to the ingestions or the lethal anæsthetic, it is not easy to determine; but this vacuolation did not occur to the same extent in other experiments, even when the animals were killed with chloroform.

All the other hormonopoietic organs appeared normal after injections of, and feeding with, extract of the pars anterior.

No abnormal appearances whatever were noted in any of the organs of internal secretion after injections of infundibulin.

[1] Renon, L., and A. Delille, *Compt. Rend. Soc. Biol.*, 1908, lxv, 499.

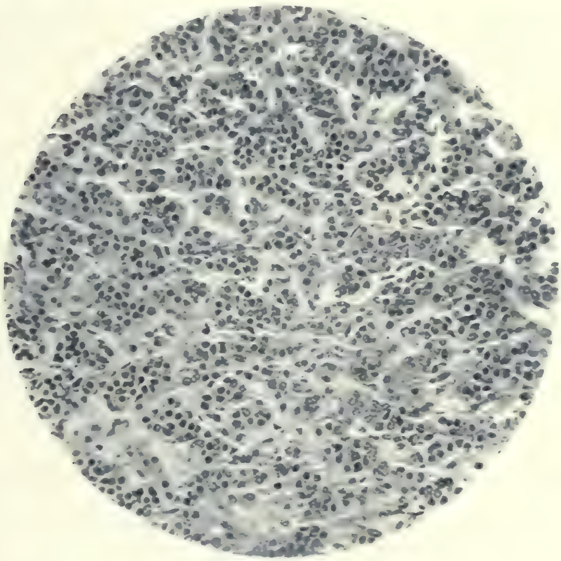

FIG. 117.

Section of the pars anterior of the guinea-pig showing lobular arrangement and chromophobia of the cells after repeated injections of an extract of the pars anterior. (*Photomicrograph.*)

× 150.

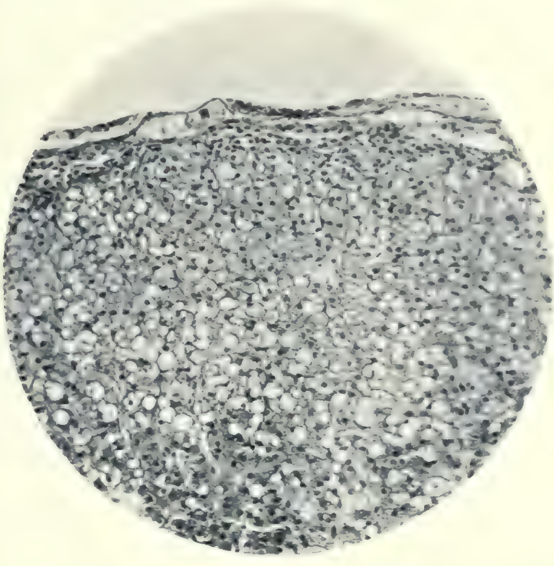

FIG. 118.

Section of the suprarenal cortex of the guinea-pig after repeated injections of an extract of the pars anterior, showing vacuolation. (*Photomicrograph.*)

× 60.

REMOVAL OF THE OTHER HORMONOPOIETIC ORGANS

Much more work has been done in regard to the results that follow the extirpation of various hormonopoietic organs. We shall consider first the changes found in the pituitary body after removal or destruction of different members of the internal secretory system; and, in the second place, we shall briefly narrate the effects produced by the removal of the pituitary body, in whole or part, upon these same organs—a subject to which reference has already been made.

The effects on the pituitary body of removal of the thyroid and thyroparathyroid apparatus

Rogowitsch[1] appears to have been the first definitely to trace some close connexion between the pituitary and the thyroid. Vincent[2] believes that the thyroid and parathyroids are closely related in regard to their functions. Most physiologists, however, look upon these organs as being independent of one another.

Finding that increased activity was produced in the pituitary by thyroidectomy, Rogowitsch came to the conclusion that the pituitary body acts vicariously for the thyroid.

Other observers subsequently confirmed these observations; and more recently Herring[3] conducted a series of experiments on the subject, and summarized his results. No changes were found by him in the anterior lobe; but there was increased activity in the cells of the pars intermedia, especially in regard to their invasion of the pars nervosa: granular, 'hyaline' or 'colloid' bodies were observed scattered throughout this portion of the pituitary, and collected together at the neck and beneath the floor of the third ventricle.

This investigator concluded, therefore, that these 'hyaline' bodies, as he called them, find their way into the third ventricle. Further, Herring noted a change in the ependymal cells lining the infundibular recess and third ventricle in the rabbit, and he observed, also, that they secreted and liberated "small, clear, globular bodies". The neuroglia, too, he states, was proliferated.

[1] Rogowitsch, N., *Zeigler's Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1889, iv, 453.
[2] Vincent, Swale, *The Internal Secretions*, Lond., 1912.
[3] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 281.

Degener and Livingston[1] have observed that removal of the thyroparathyroid apparatus in rabbits is followed by a considerable increase in the weight of the pituitary. After some months it was found that the average weight of the pituitaries in milligrammes per kilogramme of the body-weight was 11·4 for the control animals, and 17·6 for the animals previously subjected to the operation.

My own observations[2] were carried out on cats, several of which, owing to incomplete parathyroidectomy, survived for some time. Some of the animals were pregnant when the thyroid was removed, and some non-pregnant. As the results obtained appear to be constant in certain respects under similar conditions so far as the pituitary is concerned, I shall give the protocols of a few of the experiments. The extent of the changes vary, of course, with the length of time that has been allowed to elapse between the extirpation experiment and the death of the animal. In those animals which lived for some time no doubt some parathyroid tissue was left behind ; but in all definite thyroid insufficiency was produced. Pregnancy, too, seemed to accentuate the effects on the pituitary of thyroidectomy.

Experiment I.—Thyroid removal : Cat, pregnant about full-term.

October 4th. Thyroid apparatus removed.

October 6th. Animal died, with convulsions.

Interval between the operation and death : 48 hours.

Histological examination of the pituitary :

Anterior lobe. Very few large chromophobe 'pregnancy cells' to be seen : practically all the cells are eosinophil.

Pars intermedia. There is much colloid secretion in the reticulated groups of cells beneath the third ventricle. The cells of the pars intermedia lining the cleft are fused, and the appearance presented is as though the nuclei of the cells are lying in a mass of granular secretion (fig. 119).

Pars nervosa. This is compact, and is studded with granular bodies ; most have nuclei, but in some the nuclei have disappeared (fig. 120).

[1] Degener, L. M., and A. E. Livingston, *Amer. Journ. Physiol.* (*Proc. Amer. Physiol. Soc.*), 1913, xxxi, xxiv.

[2] Bell, W. Blair, *Arris and Gale Lectures : Lancet*, 1913, i, 707.

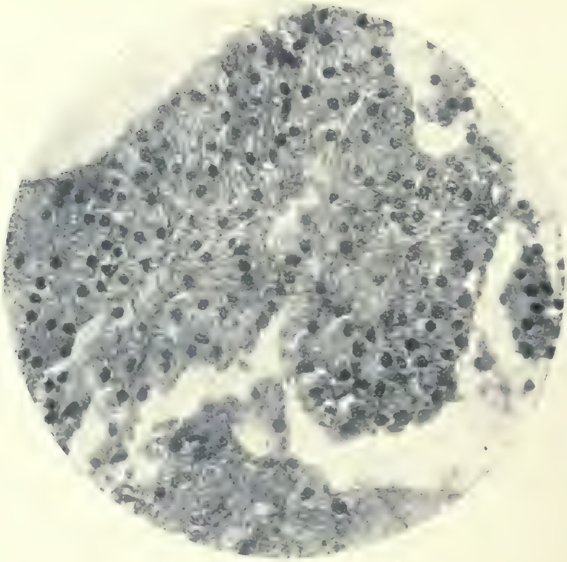

FIG. 119.

Section of the pars intermedia of the pregnant cat 48 hours after thyroparathyroidectomy, showing secretory activity. (*Photomicrograph.*)

× 250.

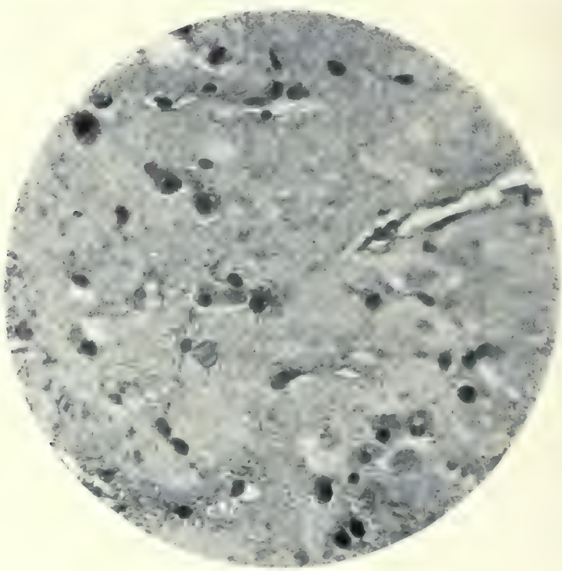

FIG. 120.

Section of the pars nervosa of the pregnant cat 48 hours after thyroparathyroidectomy, showing invasion of the pars nervosa by the cells of the pars intermedia. (*Photomicrograph.*)

× 500.

Experiment II.—Thyroid removal: Cat, pregnant nearly full-term.

October 20th. Thyroid apparatus removed.

October 23rd. Three kittens born alive. All were suckled.

November 12th. The last of the kittens died.

November 20th. Animal died.

Interval between the operation and death: 30 days.

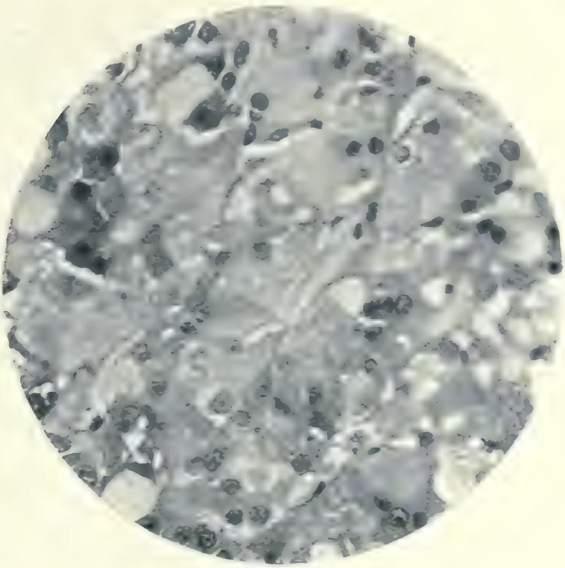

FIG. 121.

Section of the pars anterior of puerperal cat 30 days after thyroidectomy during pregnancy, showing large chromophobe cells. (*Photomicrograph.*)

× 500.

Histological examination of the pituitary:

Anterior lobe. The middle portion contains many large chromophobe 'pregnancy cells'. There is no marked eosinophilia except among the cells forming the upper and lower limits. Some empty spaces are to be seen. Under a higher magnification much secretion can be detected round the 'pregnancy cells', giving the appearance of syncytium. A few large basophil cells can also be observed (fig. 121).

Pars intermedia. The outlines of the cells are blurred; there is 'vacuolation', and great secretory activity (fig. 122).

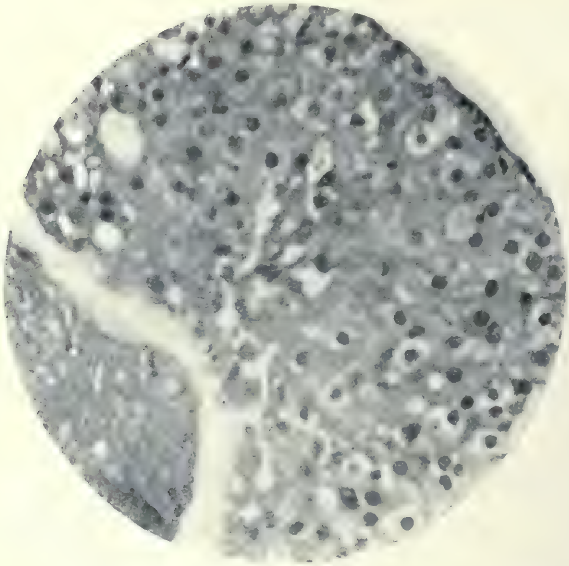

FIG. 122.

Section of the pars intermedia of the puerperal cat 30 days after thyroidectomy during pregnancy, showing 'vacuolation' and secretory activity. (*Photomicrograph.*)

× 400.

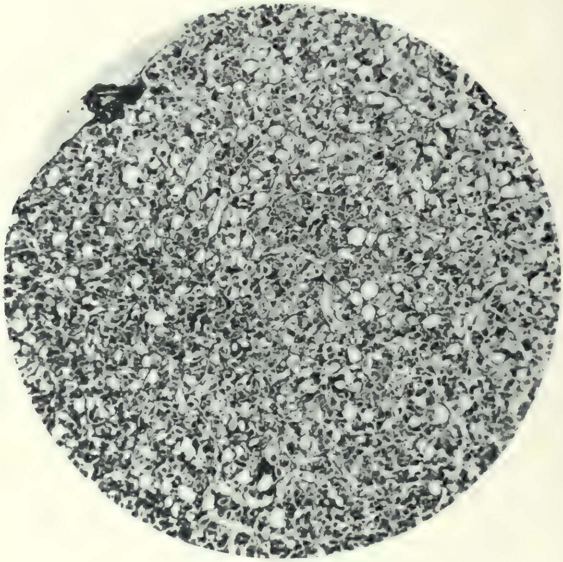

FIG. 123.

Section of pars anterior of the cat 130 days after thyroidectomy during pregnancy, showing 'vacuolation' due to excessive secretion. (*Photomicrograph.*)

× 60.

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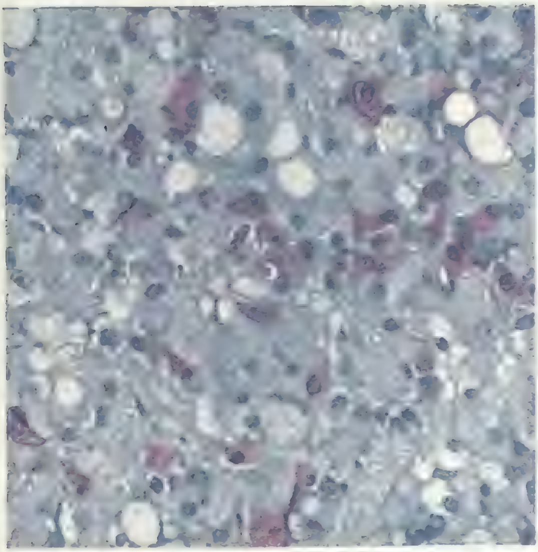

PLATE 3.

Section of the pars anterior of the cat 130 days after thyroidectomy during pregnancy. There is confluence of chromophobe cells and 'vacuolation'—probably due to accumulations of secretion—only a few scattered eosinophil cells are to be seen.

× 500

(Direct colour photomicrograph).

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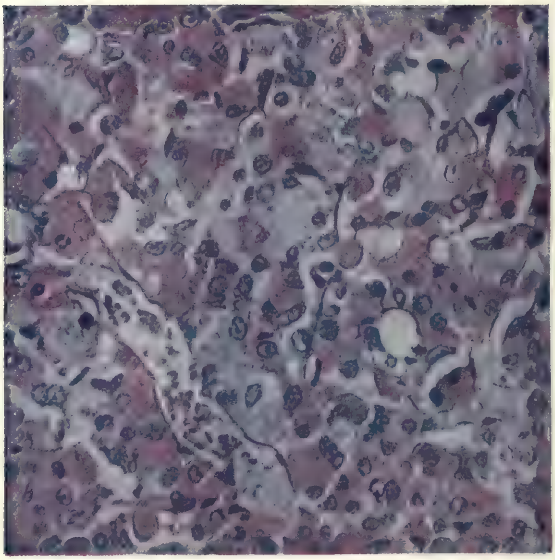

PLATE 4.

Section of the pars anterior of the non-pregnant cat 79 days after thyroidectomy, showing many large chromophobe cells lying among strongly staining eosinophils.

× 500

(Direct colour photomicrograph).

Pars nervosa. Hyaline or granular bodies are not discernible ; but the pars nervosa seems to be invaded by cells from the pars intermedia ; and at the neck the secretion of the cells is collected as if about to be passed into the nervous portion.

Experiment III.—Thyroid removal: Cat, pregnant about 20 days.

June 19th. Thyroid removed.

June 29th. Two premature kittens born.

October 24th. Animal killed with chloroform.

Interval between operation and death : 130 days.

Histological examination of the pituitary:

Anterior lobe. Under a low magnification the anterior lobe appears to be extensively vacuolated (fig. 123). The cells are chiefly chromophobe (plate 3), but there are a few scattered eosinophils. The condition of 'vacuolation' is seen to be due to excessive secretion, in some places in the cells, and in others between the cells ; and in the latter case the secretion is often surrounded by a vesicular arrangement of the neighbouring cells.

The cells of the pars intermedia are well defined and not much fused.

Pars nervosa seems to be teased out, but there is no unusual invasion by pars intermedia cells.

Experiment IV.—Thyroid removal: Cat, non-pregnant.

June 12th. Thyroid removed.

August 30th. Animal killed with chloroform.

Interval between operation and death : 79 days.

Histological examination of the pituitary:

Anterior lobe. This is largely composed of eosinophil cells; but there are many active chromophobe cells to be seen (plate 4).

Pars intermedia. There is considerable activity in the cells of the pars intermedia, and faintly staining basophil (neutrophil) secretion can be seen in the cleft (fig. 124).

Pars nervosa. This portion of the pituitary is finely reticulated, but there is no invasion by cells of the pars intermedia.

It appears, therefore, that, while there is undoubtedly an

increase in the activity of the pituitary body after thyroidectomy, the changes observed are greater in the pituitary of the pregnant animal than in that of the non-pregnant. Further, while the changes observed, if correctly interpreted, all indicate an increase of activity after thyroidectomy, the appearances vary according to the extent of thyroparathyroid insufficiency, as indicated by the immediate effect on the animal, by the length of time between the operation and death, and probably also according to the period of pregnancy.

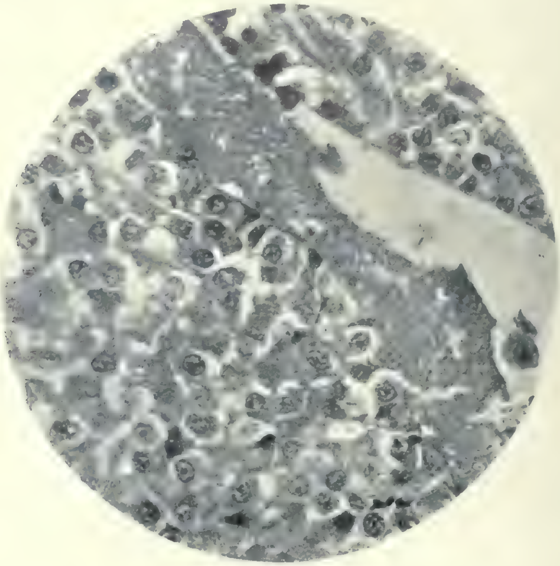

Fig. 124.

Section of the pars intermedia of the non-pregnant cat 79 days after thyroidectomy, showing secretion in the cleft. (*Photomicrograph.*) × 500.

The alterations in the pituitary as the result of thyroidectomy, as I have observed them, may be summarized as follows:—

Anterior lobe. Contrary to the opinion expressed by Herring who operated upon (? non-pregnant) dogs, cats and rabbits, I believe that definite changes do occur in the anterior lobe. These changes appear to vary from an increased eosinophilia of the cells, with scarcity of basophil cells and the presence of numerous neutrophil cells (plate 4), to a condition of great activity when the thyroid is removed during pregnancy, and the animal survives for a long period (plate 3). In the last-named circumstances

the cells of the anterior lobe become filled with secretion which may give rise to an appearance of vacuolation; and they are, also, large and for the most part chromophobe.

Pars intermedia. We find that there is considerable activity in the cells which line the cleft and in the reticulated groups at the base of the third ventricle. The cells in the reticulated portion appear always to remain discrete, and to produce neutrophil secretion, as in normal circumstances; while the cells of the pars intermedia lining the cleft secrete faintly staining granular material either into the cleft (fig. 124), or on the surface of the pars nervosa. In conditions of great activity the cells themselves always seem to fuse (figs. 119 and 122)—the nuclei appearing to lie among a mass of secretion.

The pars nervosa may contain much granular secretion in degenerating cells, or free.

I have been unable to confirm Herring's observations as to the increased activity of the ependymal and neuroglial elements.

Now, it will have been noticed that while the appearances described above all indicate a condition of increased activity, exactly the same appearances are not seen in all the instances described and illustrated; but, as I have already pointed out, I have selected examples in which the circumstances as to relative insufficiency, length of life and so on, varied. I would, however, emphasize the fact that I have found with similar conditions and in similar circumstances practically the same appearances always produced.

The interpretation of my results does not appear to be very difficult; and I hope in the explanation to throw some light on that least understood of all the problems in connexion with the pituitary—the relation of the anterior lobe to the pars intermedia and the pars nervosa.

It will have been noted that in no case were all three parts of the pituitary found in a state of excessive activity at the same time. In experiment II we have the nearest approach to this, and in this animal no granular or other secretion-masses are to be seen in the pars nervosa. In experiment III the activity of the anterior lobe is most marked; while the cells of the pars intermedia are not very active, nor is there secretion in the pars nervosa. In experiment I, in which there was acute thyroid (including parathyroid) insufficiency, as indicated by death with

convulsions in 48 hours, there was considerable activity in the pars intermedia and pars nervosa, without excessive activity in the pars anterior.

These facts all seem to point to the conclusion that the pituitary body is one organ ; and that the functional activity of the posterior lobe is dependent on the functional activity of the anterior. Further, it appears that the action is not necessarily continuous in every portion at the same time—indeed, the reverse appears to be more common. Later, I shall adduce pathological evidence in support of this hypothesis—showing that the function of each portion is dependent on the integrity of the whole.

Effects on the thyroid of partial and complete removal of the pituitary

Owing to the fact that the number of operators who have successfully excised the pituitaries of animals is very small, observations concerning the effects of removal of the pituitary upon the thyroid are limited. Allusion has already been made to this question in connexion with experimental operations on the pituitary, but for the sake of completeness the observations recorded may be briefly enumerated here.

Crowe, Cushing and Homans[1] observed a hyperplasia in the first forty-eight hours after complete removal ; and, if the animal survived the complete or nearly complete extirpation of the pituitary, a ' functional involution ' of the thyroid, with accumulation of colloid in the vesicles was noted.

I was unable in my experiments to detect the hyperplasia mentioned by Cushing. When any abnormality was noted in the thyroid it was of the nature of excessive accumulation of colloid.

In figure 125 is seen the thyroid—apparently normal, or with only slight excess of colloid—70 hours after complete removal of the pars anterior of the pituitary. According to Cushing there should have been hyperplasia.

Figure 126 shows the excess of colloid found in a case of *dystrophia adiposogenitalis* 129 days after the compression of the

[1] Crowe, S. J., H. Cushing, and J. Homans, *Bull. Johns Hopk. Hosp.*, 1910, xxi, 127.

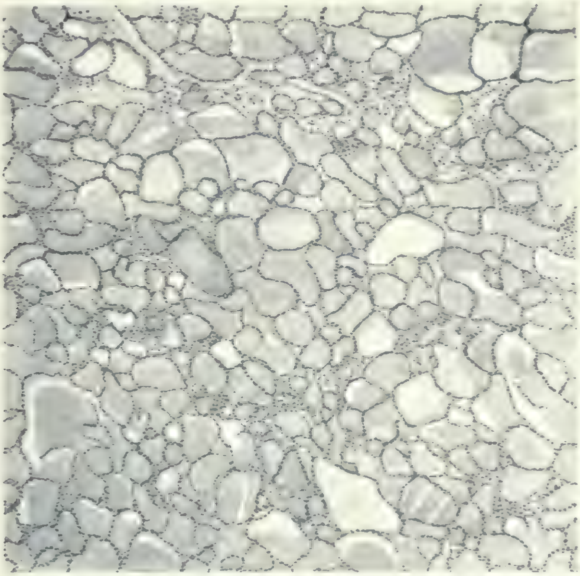

FIG. 125.

Section of the thyroid of the bitch 70 hours after total extirpation of the pars anterior. There is no departure from the normal.

× 60.

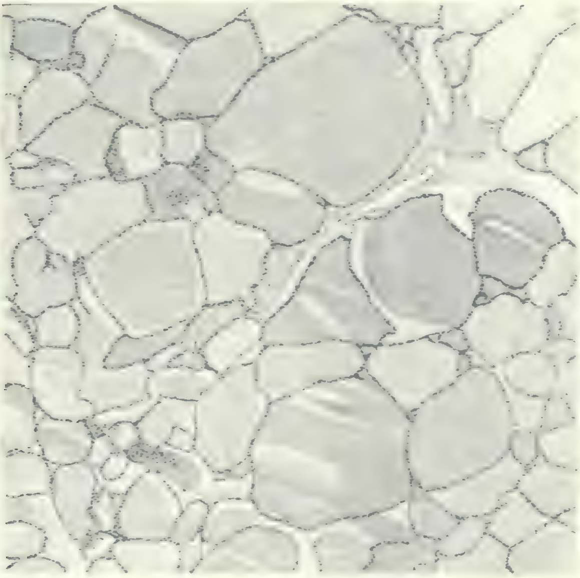

FIG. 126.

Section of the thyroid of the bitch 129 days after compression of the stalk of the pituitary. There is an abnormal amount of colloid in the vesicles.

× 60.

infundibular stalk. In this case the size of the thyroid was observed to be twice that of the normal organ.

Neither removal of the whole pituitary nor of the posterior lobe produces any change in the thyroid that can definitely be pronounced to be abnormal.

Effects on the pituitary of removal of the ovaries

That there is a close interrelation between these two members of the internal secretory system has long been known, and many interesting hypotheses have been formed.

Mayer[1] and others believe that the pituitary is able to act vicariously for the ovaries, since it enlarges in pregnancy and after castration. It has even been suggested that the enlargement of the hands and lips sometimes observed in pregnancy is due to excessive pituitary secretion following ovarian insufficiency. So, too, hemianopia, which on rare occasions is seen in pregnancy, has been attributed to the pressure of the enlarging pituitary on the optic tract. As we have already noted, the hyperplasia that occurs during gestation is chiefly due to large chromophobe cells of the anterior lobe.

Degener and Livingston[2] have not found any increase in the weight of the pituitary after castration.

I have castrated many female cats, and many months subsequently have examined the pituitary bodies. Examples of the typical effects on the pituitary are shown in the following protocols :—

Experiment I.—Ovarian removal : Cat, non-pregnant.

February 21st. Ovaries removed.

October 23rd. Animal killed with chloroform.

Interval between operation and death : 245 days.

Histological examination of the pituitary body :

Anterior lobe. There is a very large preponderance of eosinophil cells ; so much so that most fields examined show only eosinophils (plate 5).

Pars intermedia. The cells appear fused. There are

[1] Mayer, E., *Arch. f. Gyn.*, 1910, xc, 600.

[2] Degener, L. M., and A. E. Livingston, *Amer. Journ. Physiol.* (*Proc. Amer. Physiol. Soc*), 1913, xxxi, xxiv.

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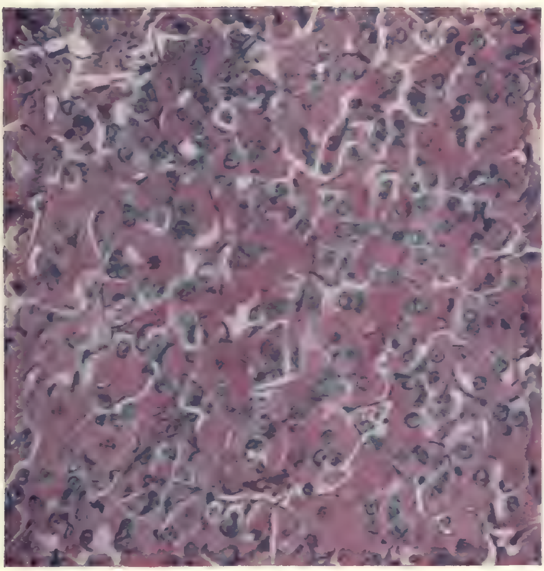

PLATE 5.

Section of the pars anterior of the non-pregnant cat 245 days after oöphorectomy, showing intense eosinophilia of the cells.

× 500

(*Direct colour photomicrograph*).

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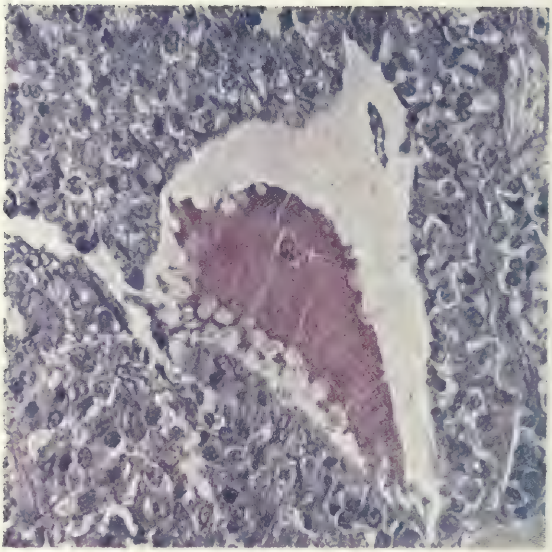


PLATE 6.

Section of the pars intermedia of the non-pregnant cat 245 days after oöphorectomy, showing eosinophil colloid.

× 500

(Direct colour photomicrograph).

colloid-vesicles, and in one place a colloid-cyst. The colloidal material is eosinophil (plate 6).

Pars nervosa. This structure has a teased-out appearance. There are no granular or 'hyaline' bodies.

Experiment II.—Ovarian removal: Cat, non-pregnant.

April 24th. Ovaries removed.

November 20th. Animal killed with chloroform.

Interval between operation and death: 210 days.

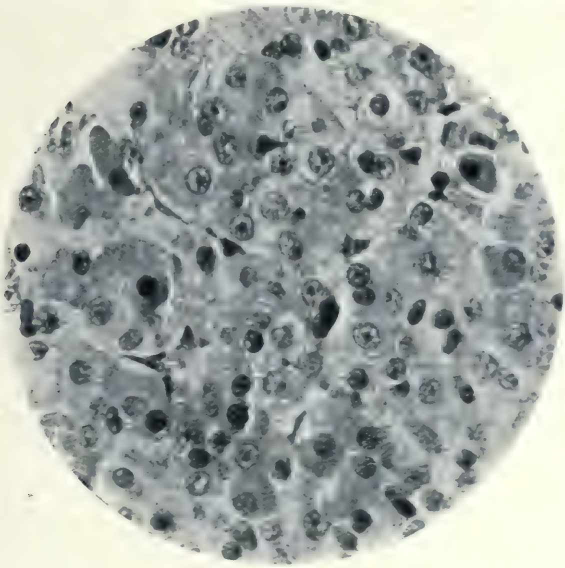


FIG. 127.

Section of the pars anterior of the non-pregnant cat 210 days after oöphorectomy showing eosinophils, large chromophobe cells with clear nuclei, and a few basophils. (*Photomicrograph.*)

× 500.

Histological examination of the pituitary body:

Anterior lobe. This is largely composed of eosinophil cells; but there are many active chromophobe cells, and at the periphery some faint, and a few dark, basophil cells (fig. 127).

Pars intermedia. There is considerable degree of fusing of the cells; and there is much eosinophil secretion, especially in the reticulated portion (fig. 128).

In the compact portion at the neck are to be seen coarsely granular cells, exactly resembling the nucleated

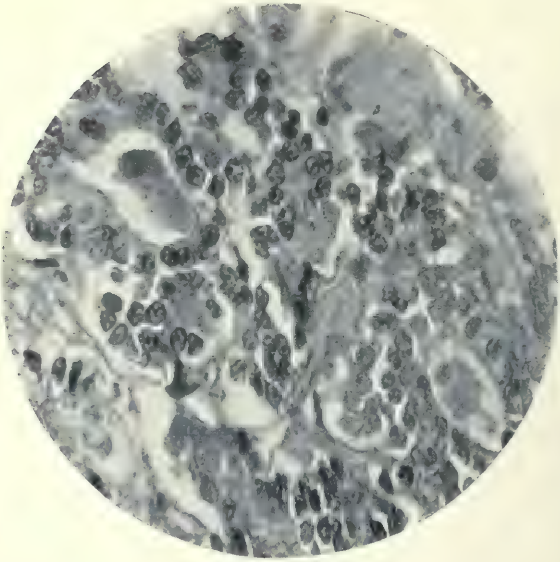


FIG. 128.

Section of the reticulated part of the pars intermedia in the non-pregnant cat 210 days after oöphorectomy, showing eosinophil secretion.

× 500.

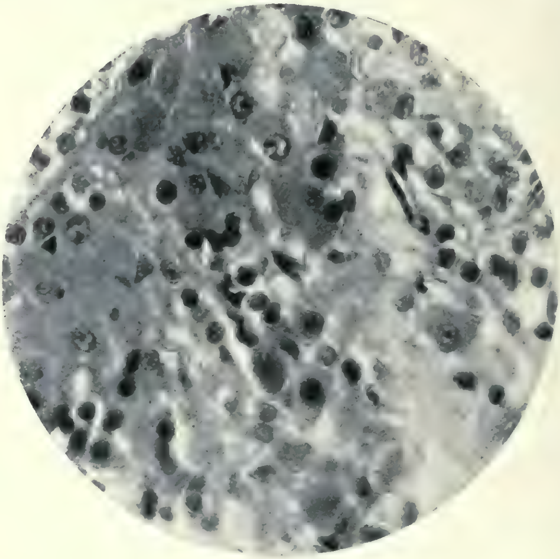


FIG. 129.

Section of the pars posterior of the non-pregnant cat, at the junction of the partes intermedia and nervosa, 210 days after oöphorectomy, showing secretion and granular bodies. (*Photomicrograph.*)

× 500.

granular cells sometimes seen in the pars nervosa, and much secretion (fig. 129).

Pars nervosa. There are no granular bodies.

From an examination of a large number of specimens I am forced to the conclusion that although there is considerable increase in the activity of the anterior lobe and pars intermedia of the pituitary after oöphorectomy, yet this is not so well marked as after removal of the thyroid. In some cases, such as in cat 5 of my series, which was killed after an interval of 208 days, there was no divergence from the normal; consequently my observations are opposed to the hypothesis, which many authorities have sought to establish, that genital atrophy is the primary cause of acromegaly (hyperpituitarism). Fichera[1] believes, as the result of his experiments, that removal of the ovaries causes a change in the anterior lobe analogous to that produced by pregnancy. My experiments give some evidence of this in the fact observed that the chromophobe cells present seem to be large and active. It is unsettled, however, whether removal of the ovaries produces a permanent change in the pituitary, although it is certain that the immediate effect of oöphorectomy is to cause an increase in the secretory activity of the anterior lobe and of the pars intermedia, especially in regard to the eosinophil cells.

The effects on the ovaries of partial removal of the pituitary

As we have seen, the work of Paulesco[2] and of Crowe, Cushing and Homans[3] demonstrated beyond doubt that the removal of a large portion of the anterior lobe may produce genital atrophy. These observers state that in the ovaries the follicles cease to develop, and that subsequently the uterus and other parts of the genital tract undergo atrophy.

Degeneration is also stated to be produced in the germinal cells of the testes after the removal of the major portion of the pars anterior in dogs.

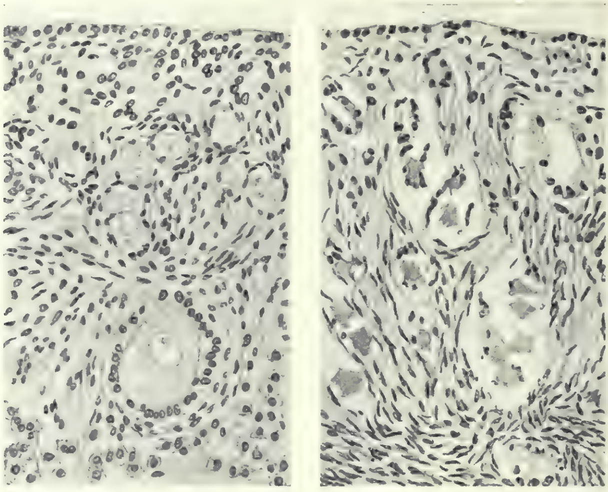
[1] Fichera, G., *Policlinico*, Rome, 1905, xii, 250, 299 and 319; also 1910, xvii, 333.

[2] Paulesco, N. C., *L'hypophyse du cerveau*, Paris, 1908.

[3] Crowe, S. J., H. Cushing and J Homans, *Bull. Johns Hopk. Hosp.*, 1910, xxi, 127.

In connexion with my own experimental operations on the pituitaries of bitches, I took the precaution of removing pieces of one ovary and the uterus before operating on the pituitary. In this way I had a specific control in each case with which to compare the organs subsequently to operation.

I usually found[1] that profound changes in the ovaries followed extensive partial removal of the anterior lobe (figs. **130, A**



A B

Fig. 130.

Sections of the ovaries of the bitch before (A) and 210 days after (B) partial removal of the pars anterior.

× 200.

and B) and compression or separation of the stalk (figs. **131**, A and B). The primordial ova undergo a hyaline degeneration: instead of showing chromatin fibres with translucent interstices, after operation the whole ovum becomes opaque and structureless. The epithelium of the Graafian follicles degenerates and disappears, leaving an empty space in the place previously occupied by the follicles. The stroma becomes dense and fibrous; and I found a total disappearance of the interstitial cells (figs. **130B** and **131B**).

In some of my experiments after partial resection of the anterior lobe the ovaries and uterus showed no retrograde

[1] Bell, W. Blair, *Quart. Journ. Exp. Physiol.*, 1917, xi, 77.

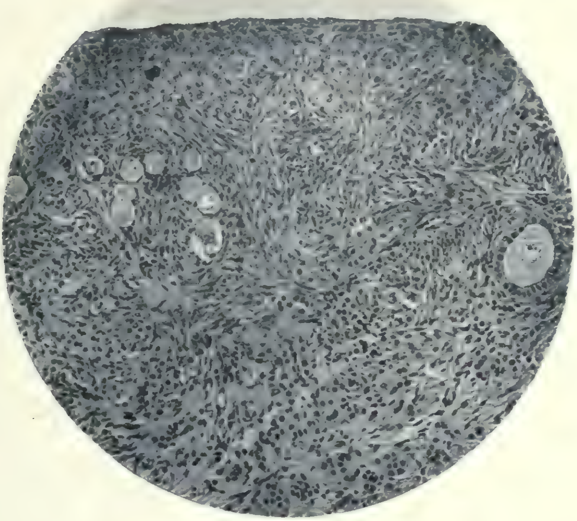


Fig. 131a.

Section of the ovary of the bitch before operation. (*Photomicrograph.*) × 120.

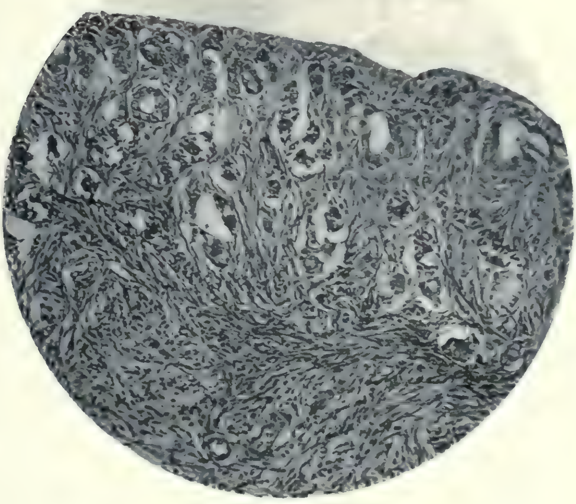
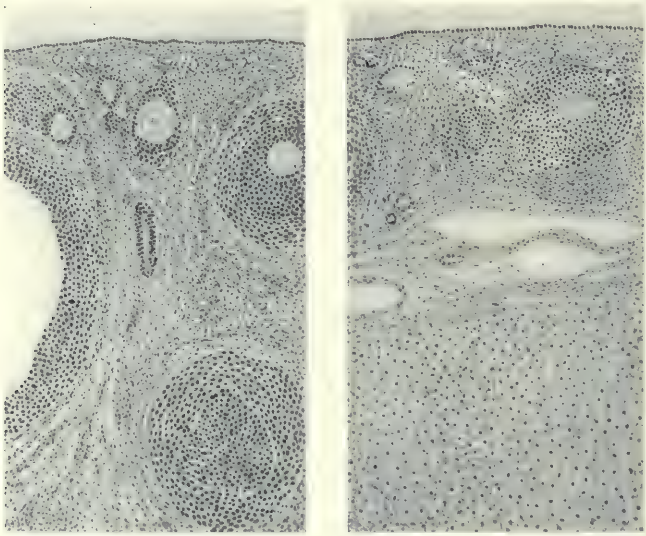


Fig. 131b.

Section of the ovary of the same bitch 128 days after separation of the stalk of the pituitary. (*Photomicrograph.*) × 120.

changes, although possibly they did not develop to the normal extent in the interval between operation and death.

Removal of the posterior lobe alone or with a small portion of the anterior lobe does not affect the development of the ovaries in the slightest degree: they go on to maturity in a normal



A B

FIG. 132.

Sections of the ovaries of the bitch before (A) and after (B) removal of the pars posterior of the pituitary. The lower part of B is occupied by cells of a corpus luteum.

× 60.

manner (figs. 132, A and B); and in one of my cases the bitch came 'on heat', and took the dog, but without becoming pregnant.

Effects on the pituitary of removal of the suprarenals

Since removal of both suprarenals is always fatal in a few days to the larger animals, such as the cat, rabbit and dog, it is impossible to obtain experimental evidence, except in regard to acute results, from this procedure.

I have, however, removed one suprarenal from cats and rabbits in the hope of producing insufficiency. This I was unable to do to any obvious or marked extent except in two cases. In a few of my experiments I first removed one suprarenal, and

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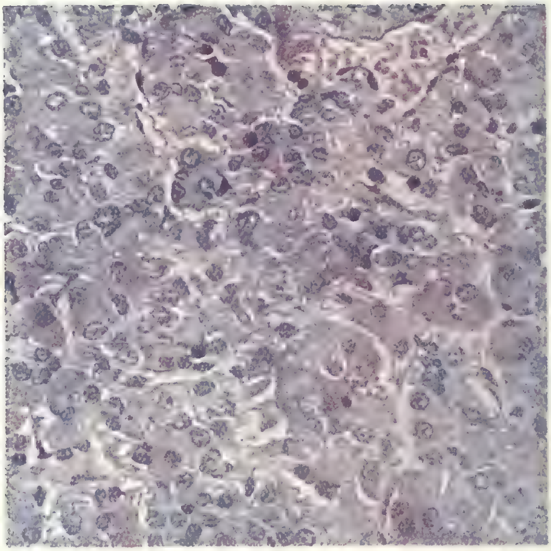

PLATE 7.

Section of the pars anterior of the non-pregnant cat 36 hours after the removal of both suprarenals. The cells for the most part are chromophobe, but here and there eosinophil cells are to be seen.

× 500

(Direct colour photomicrograph).

subsequently the second. This last operation was always followed by the death of the animal. In some of these cases I observed changes in the pituitary which were probably the result of suprarenal insufficiency[1].

The following are illustrative experiments :—

Experiment I.—Suprarenal removal : Cat, non-pregnant.

September 11th. Both suprarenals removed.

September 13th. Death occurred in spite of careful nursing and keeping the animal in a warm temperature.

There were tremors and great muscular weakness.

Interval between the operation and death : 36 hours.

Histological examination of the pituitary :

Anterior lobe. There is a large proportion of chromophobe cells, with a comparatively moderate number of eosinophil cells (plate 7). In many places the nuclei are small and darkly stained, and they stand out sharply.

Pars intermedia. The cells are discrete ; that is to say, they are not fused. The nuclei stand out prominently ; they are small and darkly stained (fig. 133). A few granular bodies can be seen among the cells of the pars intermedia.

Pars nervosa. The nervous portion is invaded by the cells of the pars intermedia ; and the appearance produced is that of nuclei, with the cell-protoplasm lost, stranded among the neuroglia-cells (fig. 134).

Experiment II.—Suprarenal removal : Cat, non-pregnant.

September 18th. Left suprarenal removed.

November 6th. All but the very small fragment of the right suprarenal removed.

November 8th. Animal died.

Interval between first operation and death : 51 days.

Histological examination of the pituitary :

Anterior lobe.—There is a large proportion of chromophobe cells, with fewer eosinophil cells than in the first experiment. The nuclei are small, round and darkly stained, and they appear to stand out from the surrounding cell protoplasm (fig. 135).

Pars intermedia.—The cells are not fused, and their nuclei stand out very prominently (fig. 136).

Pars nervosa.—This portion is much invaded by the

[1] Bell, W. Blair, *Arris and Gale Lectures : Lancet*, 1913, i, 937.

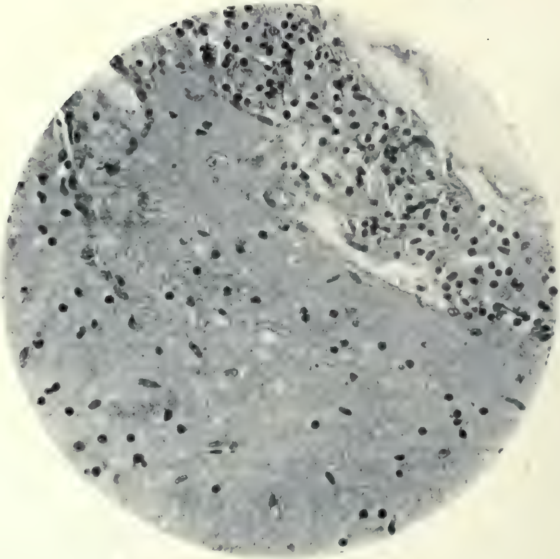

FIG. 133.

Section of the pars posterior of the cat 36 hours after removal of both suprarenals, showing invasion of the pars nervosa by the cells of the pars intermedia. (*Photomicrograph.*) × 140.

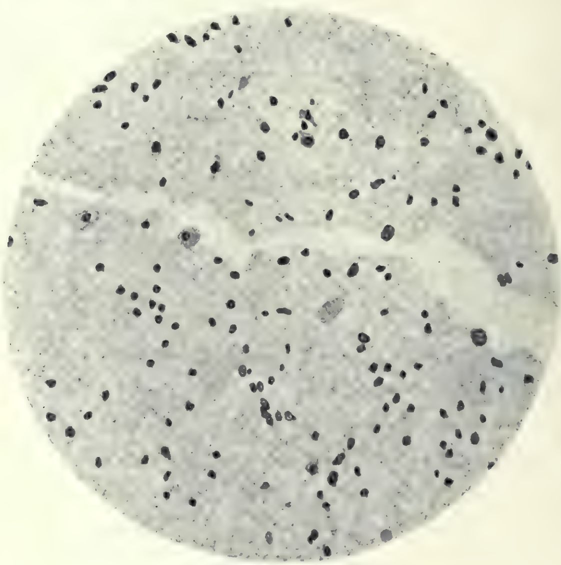

FIG. 134.

Section of the pars nervosa of the pituitary of the cat 36 hours after removal of the suprarenals, showing invasion of the pars nervosa by cells from the pars intermedia, and the stranding of their nuclei. × 200.

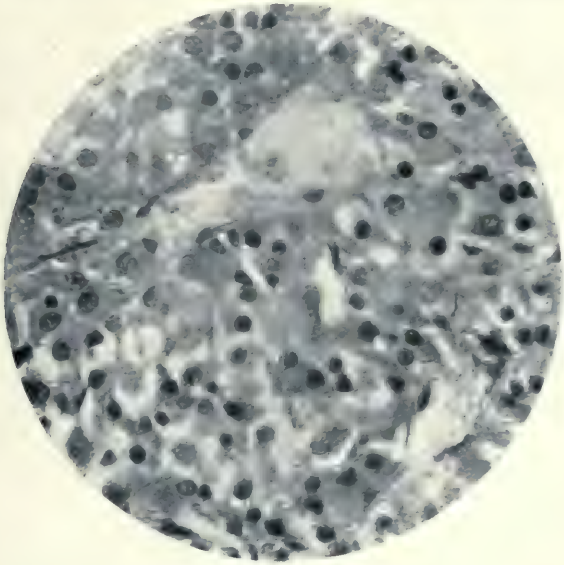

FIG. 135.

Section of the pars anterior of the cat after removal of the suprarenals, showing chromophobia of the cells, the nuclei of which show chromatosis. (*Photomicrograph.*) × 400.

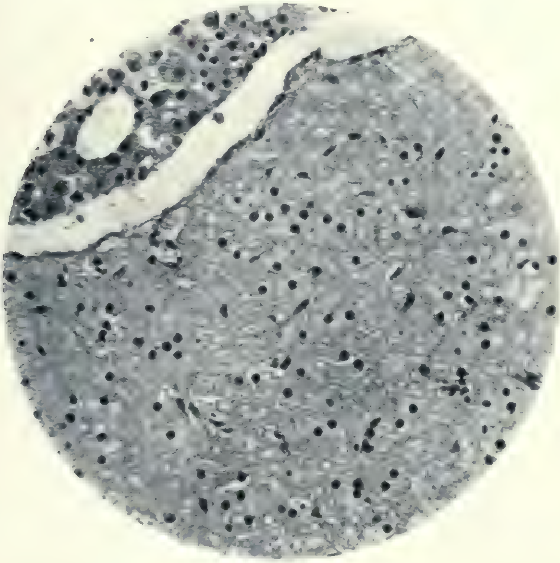

FIG. 136.

Section of the pars posterior of the cat after removal of the suprarenals, showing well-defined cells in pars intermedia, and invasion by these cells of the pars nervosa, and the stranding of the nuclei. (*Photomicrograph.*)

× 140.

cells of the pars intermedia (fig. 136), which present an exactly similar appearance to that seen in the former case (fig. 133).

The changes, then, in the pituitary of the cat that appear constant with suprarenal insufficiency, acute or chronic, are, first, an increased chromophobia of the cells of the pars anterior; second, a peculiar smallness and chromatosis of the nuclei, to some extent in the anterior lobe but most definitely in the pars intermedia, the cells of which are discrete; and third, a rapid and extensive invasion of the pars nervosa by the cells of the pars intermedia. Many of these cells appear to lose their cell-protoplasm, and the nuclei in consequence are left stranded (figs. 133, 134 and 136).

Effect of removal of the pituitary on the suprarenals

Exact observations from this point of view have not been obtained. Cushing[1] states that in experimental forms of hyper-pituitarism (presumably injection experiments, but details are not given) there is a condition of vacuolation of the zona fasciculata of the suprarenal cortex, as I have found after ingestions of an extract of the anterior lobe; but this author also states that the same condition is observed after extirpation of the pituitary. In my own experiments on the pituitary I was unable to detect definite changes in any part of the suprarenals after operation.

I have seen this lipoid (?), or secretory, change, mentioned by Cushing, after removal of the ovaries, and during pregnancy; so, as the extent of it varies in different individuals of the same species in normal circumstances, any specific cause assigned to such a condition must be received with caution. It has, too, been stated that a similar change occurs in the secretory and collecting tubules of the kidney after extirpation of ductless glands; and I myself have observed this after some of my experiments, but as I subsequently found the same change in the kidneys of control animals, especially when they had been killed with chloroform, I was compelled to acknowledge the absence of specific causation. These vacuolations require much more

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

careful observation by means of differential stains, before we can discuss them with profit. Meanwhile, I have no suggestions to make as to the exact nature of the condition, which is probably less abnormal in animals than is usually believed.

The pituitary and the other internal secretory organs

There is a certain amount of material available concerning the interrelationships between the pituitary and the pancreas and thymus.

Pancreas.—Cushing and his fellow-workers[1] first advanced the view that the carbohydrate-tolerance observed in hypopituitarism is due to disturbance of the internal secretion of the pancreas. Later, after more pathological experience, Cushing withdrew this opinion and attributed the tolerance to insufficiency of the posterior lobe[2].

It appears, however, that even the last view is not entirely correct ; consequently the results of the researches that are now being conducted by Cushing and his colleagues on this subject are awaited with interest.

In my experiments on the pituitaries of dogs I always found the pancreas normal, but in an actively secreting state, subsequently to the operation. Sweet and Allen[3] lay particular stress on a similar finding.

I have already referred to the effect of injections of infundibulin on pancreatic secretion (p. 119).

Pancreatectomy is said by Cushing[4] to produce changes in the posterior lobe of the pituitary. This observation is, I believe, unconfirmed.

Thymus.—Very little is known from an experimental point of view of the relationship between the thymus and the pituitary. In my experiments on the pituitary I found in most cases, regardless of the actual lesion, that the thymus was in an active state, as indicated by the embryonic and unwhorled

[1] Goetsch, E., H. Cushing and C. Jacobson, *Bull. Johns Hopk. Hosp.*, 1911, xxii, 165.

[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[3] Sweet, J. E., and A. R. Allen, *Ann. Surg.*, 1913, lvii, 485.

[4] Cushing, H., *Amer. Journ. Med. Sci.*, 1910, xxxix, 473.

character of the epithelium in Hassall's corpuscles (fig. 137)—a normal condition in young animals.

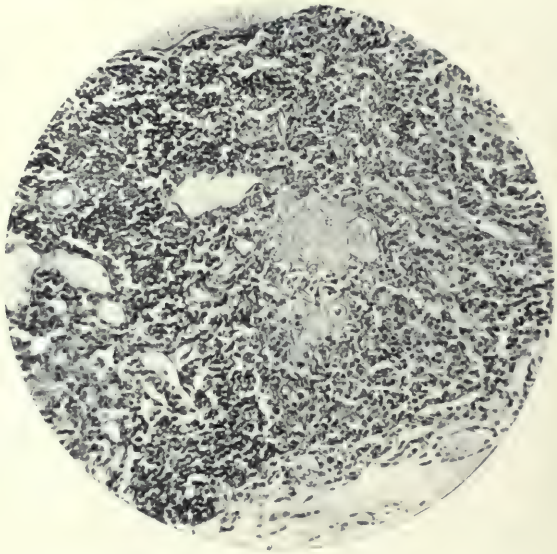

Fig. 137.

Section of the thymus of the bitch, showing unwhorled epithelial cells. (*Photomicrograph.*) × 120.

DISCUSSION OF THE RESULTS OF REMOVAL OF THE VARIOUS HORMONOPOIETIC ORGANS

The interpretation of all these experimental facts is not easy, and involves a short reconsideration of the whole question of increased activity in the pituitary.

As already stated, I believe that the three types of cells found in the anterior lobe represent different phases of secretory activity. If there be not much immediate demand for the secretion of the anterior lobe, in the higher mammals a basophil condition of some of the cells is found. From these cells basophil colloid is formed for storage purposes. After yielding up their secretion the basophil cells, as we have seen, appear as shrunken chromophobe cells. These in time become eosinophil, before ultimately again becoming basophil.

Now, the greatest demands on the secretion of the anterior lobe occur normally in pregnancy, and experimentally after removal of the thyroids and suprarenals. In both circumstances

we find what may be called ' active chromophobe ' cells—chromophobe cells, that is, which deliver up their secretion without going through the further phases of eosinophilia and basophilia.

Next in secretory activity is the phase of eosinophilia which is an intermediate condition, and, as a result, many eosinophil cells are usually present.

After removal of the thyroid, especially when the condition of insufficiency is chronic, the preponderance of eosinophil cells is most pronounced. In such circumstances we may conclude that the demand for secretion is not very urgent, and there is time for fully formed, normal, secretion to be delivered.

There can be little doubt that the secretion of the ' pregnancy cells ' and of the artificially produced ' active chromophobe ' cells is similar, and is an emergency substance. And since in these circumstances the secretion is abstracted from the cells as fast as it is formed, there is no collapse of the cell—they remain ' on duty ', as it were. If the demand be less urgent eosinophilia develops in the contents of the cells. This is normally the active condition of the cells which deliver the secretion of the anterior lobe ; while in times of plenty in the higher mammals the further phase of basophilia develops. These basophil cells eventually burst, basophil colloid is poured out and the collapsed cells represent the shrunken chromophobe cells, as already stated.

These points have been reiterated because it is important to emphasize them, and to show their bearing on the present discussion.

If my observations be correct they afford evidence concerning the ' secretory-phase hypothesis '—if so it may be called—in which many believe, but which has not been previously described in similar detail.

These observations offer, too, the only explanation of the fact that basophil cells do not occur prominently in the lower mammalian orders in which no doubt the anterior lobe is normally more active than in higher orders.

With regard to the number of nuclei—apparently bereft of cellular protoplasm—in the pars nervosa after the production of suprarenal insufficiency, it is probable that the protoplasm and its contained secretion have been rapidly utilized before the nuclei themselves have had time to disappear. This is borne out by the fact, previously recorded, that the granular masses

of secretion not infrequently seen in the pars nervosa in normal circumstances, at first possess nuclei which subsequently disappear.

Thus far, therefore, monoglandular removals have helped us to solve some of the mysteries concerning the physiology of the pituitary body. Later, we shall consider this same question of the internal secretion in relation to the pathology of this organ.

It would have been a satisfactory conclusion to this section, concerning the interrelationship between the pituitary and the rest of the hormonopoietic system, if it had been possible to give a definite and lucid exposition of the exact dependence each has on the secretion of the rest. Our information, however, is too fragmentary and unsatisfactory for such a disquisition, yet I cannot help feeling that the day is not far distant when we shall be in a position to describe this part of the subject with comparative comprehensiveness and certainty.

Too little attention has been paid to those secretory organs which do not easily and certainly yield so-called 'physiologically active' secretions—that is, an active extract which will produce an immediate physiological effect. No doubt we have been hampered by technical and experimental difficulties, such as are encountered in the removal of certain parts of organs—for example, the suprarenal cortex.

Meanwhile there are two other lines of very profitable investigation, one physiological and the other pathological. We require more information in regard to the activation of the so-called 'inactive' organs: in other words, we must identify the hormones. It is probable that the secretions of these so-called 'inactive' organs are active enough when combined with, or stimulated by, one or other, or by several, of the other internal secretions. In seeking to discover the reason of the uncertainty of action of the ovarian extract I found that this preparation is much more active when thyroid extract is administered at the same time. The second line of investigation is an easy one. It consists of careful histological examinations of the whole hormonopoietic system in all cases of disease of one or more members of the series. Many deaths occur yearly from these lesions, yet there exists no study of importance from this pathological point of view.

THE EFFECTS OF INOCULATIONS WITH BACTERIA

ALTHOUGH a certain amount of work has been done from the clinicopathological point of view in regard to the changes in the pituitary as a result of infections, extremely little experimental work has been carried out. Delille[1] refers to the striking hyperplastic changes to be observed in the pituitaries of rabbits after inoculations with typhoid bacilli.

I have conducted a series of inoculation experiments in guinea-pigs with tubercle, colon bacilli, staphylococci and streptococci.

In figures 63 (p. 86) and 138 are seen the normal appearances of the pars anterior of pregnant and non-pregnant guinea-pigs, respectively. In the pregnant guinea-pig there is marked lobulation—the so-called adenomatous disposition—of the chromophobe cells (fig. 63). In the non-pregnant animal (fig. 138) the cells present a more uniform appearance of eosinophilia. In figure 139 is shown the pars anterior of a non-pregnant guinea-pig which had received 13 injections of an emulsion of colon bacillus. It will be observed that there is hyperplasia with considerable increase in cell-contrast and definition. Many of the cells are chromophobe, and vacuoles containing secretion are plentiful; the appearance, indeed, is not unlike that seen in the pars anterior after thyroidectomy.

Staphylococcal infections produce, in most cases, a more advanced change. The blood-sinuses appear very full, and in parts of the pars anterior there are necrosis and disappearance of many of the cellular elements. For the most part the eosinophil cells are few, and where necrosis is not complete faintly staining chromophobe cells are plentiful. A peculiar feature is the survival of deeply basophil cells—normally absent in the

[1] Delille, A. (quoted by Cushing, H., *The Pituitary Body and its Disorders*, 1912).

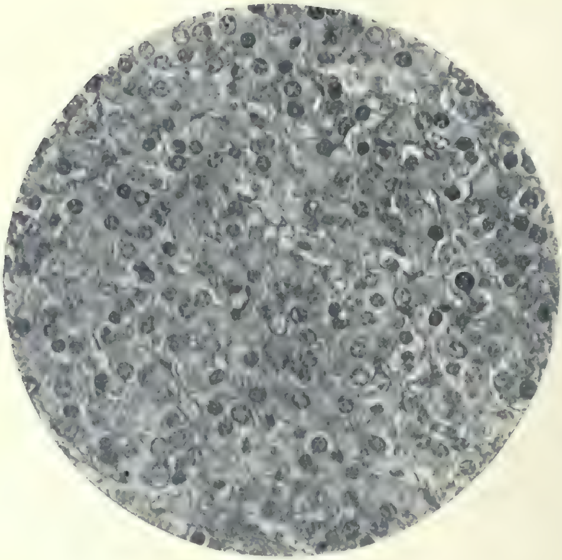

FIG. 138.

Section of the pars anterior of the normal non-pregnant guinea-pig. (*Photomicrograph.*)

× 400.

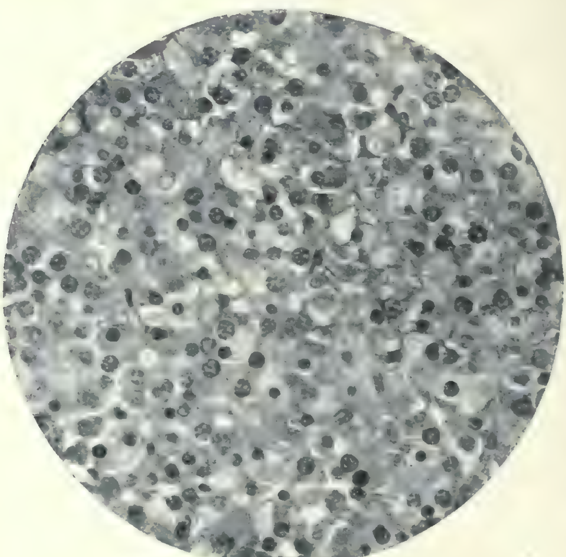

FIG. 139.

Section of the pars anterior of the guinea-pig after 13 injections of an emulsion of colon bacillus, showing chromophobia with increased secretory activity. (*Photomicrograph.*)

× 400.

guinea-pig—which consequently appear in some cases to dominate the picture (fig. 140).

In the series of animals dying from tuberculosis, or killed when deeply affected by this disease, three were pregnant and six were non-pregnant. It is important always to take into consideration the presence or otherwise of pregnancy in female animals, since the normal changes during gestation are considerable, as already indicated. In the non-pregnant animals the cells of the anterior lobe present a greater degree of chromophobia

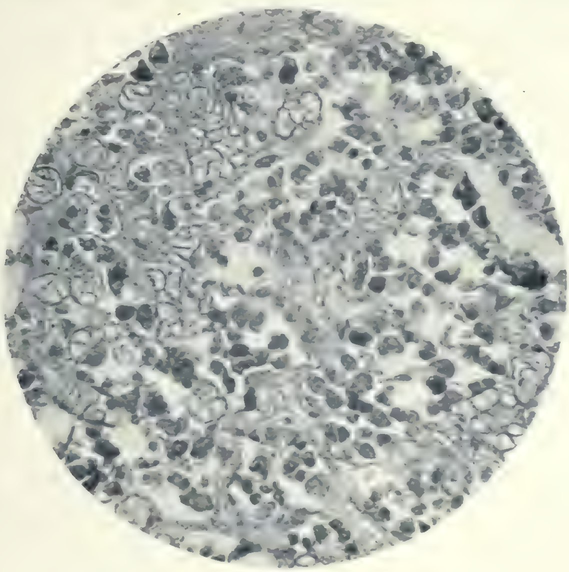

Fig. 140.

Section of the pars anterior of the guinea-pig after injections of an emulsion of staphylococcus, showing necrosis with survival of basophil cells. (*Photomicrograph.*) × 400.

than normal; and in the pregnant animals the chromophobe cells are more numerous, more indistinct, and apparently larger than normal. The nuclei appear brightly and distinctly stained against a hazy background of cell-cytoplasm. But on the whole the tubercle bacillus affects the pars anterior less than is the case with the other organisms.

In the streptococcal cases there is very well-marked chromophobia, and in the non-pregnant animals the large chromophobe cells resemble those seen in pregnancy. The appearance

of blurring, also, may be an indication of increased activity, if it be not a sign of commencing degeneration.

The changes, then, that may occur in the pituitary as the result of experimental inoculation of bacteria vary from hyperplasia of the eosinophil cells to chromophobia with considerable increase in activity. The later necrotic changes are due to direct infection of the gland and thrombosis of the vessels.

In no case was any change observed in the pars nervosa, but in the pars intermedia there usually appeared to be considerable activity in the cells—that is, fusion of the cell-bodies; this, of course, we should expect in view of the changes in the pars anterior.

THE INTERPRETATION OF PATHOLOGICAL PROCESSES AFFECTING THE NORMAL PHYSIOLOGY

THE method of studying physiological processes through 'Nature's experiments' is one of the greatest value, but unfortunately is not used to any great extent by physiologists or clinicians, probably because as a rule neither class of investigator is sufficiently acquainted with the work and requirements of the other.

I shall deal very briefly with the subject here, for the facts on which my arguments will be based are set out in more detail in the next part of this work.

Infections

Infections, whether local or general, cause hyperplasia in the pars anterior; consequently it has been presumed that one of the normal functions of the pituitary is to neutralize toxins which may be circulating in the blood.

Diseases associated with pregnancy

In the so-called toxæmias of pregnancy we shall observe abnormal conditions of the pituitary. For the most part these indicate that this organ is not in the high state of activity that is usual during pregnancy. Possibly this leads to a condition of acidosis; for one of the normal functions of the pituitary is the retention of alkaline bases in the tissues, a state of affairs which is directly opposed to acid intoxication.

Diseases of the hormonopoietic system

We observe in pathology, as in physiology, close relationships between the pituitary and the other organs of internal secretion.

Furnivall[1] found only one normal thyroid in twenty-four cases of pituitary lesions which he had collected from the literature, and in which complete records were given. Cushing[2] in fifteen cases found marked excess of colloid in all the thyroids. Of these fifteen cases the pituitary condition in all but a single case was one of insufficiency. No changes were found in the parathyroids.

It does not appear, therefore, that the thyroid acts vicariously for the pituitary, as has been suggested by some. On the one hand, there is evidence, already mentioned, that whole-gland pituitary extract stimulates the activity of the thyroid. On the other hand, I have found that infundibulin has a beneficial effect on hyperthyroidism.

Schönemann[3], in an investigation of eighty-five cases of goitre, found 'marked alterations' (no details are given) in the pituitary.

I myself have observed changes in the pituitary in diseases of the thyroid which indicate that the pars anterior acts in a complementary fashion so far as the thyroid is concerned, and that the activity of the former is related to the relative insufficiency of the latter.

Regarding the relation of the pituitary to the gonads, we have evidence that in acromegaly there may be stimulation of the male genital organs. This, however, is only observed in the early stages of the disease. I shall mention a case later in which hypertrophy of the clitoris occurred in a woman with this disease.

In view of the physiological and pathological evidence at our disposal we may assume that lesions and removal of the pituitary have a far more pronounced effect upon the genital glands than the extirpation of these organs has upon the pituitary.

The pathological evidence of a relationship between the pituitary and suprarenals is very slight, although it is impossible not to recognize in many cases of hyperpituitarism a pluriglandular syndrome, for acromegaly may be accompanied by manifestations resembling Addison's disease.

[1] Furnivall, P., *Trans. Path. Soc.*, 1898, xlix, 204.

[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[3] Schönemann, A., *Virchow's Arch. f. Pathol. Anat. u. Physiol.*, 1892, cxxix, 310.

It is possible, therefore, that in hyperpituitarism (acromegaly), in which there is an excess of secretion, the suprarenals become inactive, and that in hypopituitarism (*dystrophia adiposogenitalis*) suprarenal activity increases. This, at any rate, is the interpretation Cushing places on the results of his extirpation experiments. In my own I failed to observe definite changes in the suprarenals after operations on the pituitary; and I do not think the second conclusion is justified by the clinical evidence at our disposal in regard to hypopituitarism.

We have very little pathological information that throws any light on the normal relationships of the pancreas, the pineal and the thymus to the pituitary—certainly nothing that calls for discussion here.

§ iii. COMPARATIVE PHYSIOLOGY

VERY few words are necessary to describe the comparative physiology of the pituitary.

We have seen that in all vertebrates higher than the elasmobranchs there is a definite pars nervosa; and it has been found that extracts made from this structure, or from the whole gland containing this part, are active in all the respects already described. For our information on this subject we are chiefly indebted to the work of Herring[1]. This observer has, moreover, noted the extremely interesting fact that although the pituitary of the skate (elasmobranch) contains no pars nervosa, and that, therefore, an extract of the gland gives none of the well-known pressor effects associated with the action of infundibulin, yet the extract made from the epithelial portion has a definite augmentative effect on the flow of milk from the mammæ of a lactating animal.

This same result was obtained with an extract made from the epithelial portion of the pituitary of the cod, but there was also a rise in blood-pressure, and this, as Herring justly says, may indicate the inclusion of some of the extract of the pars nervosa which is present in teleosts.

Further investigations are required to confirm and extend these interesting observations, especially in regard to the acquisition of evidence which might further indicate that it is the epithelial portion which dominates the functions of the pituitary.

The investigations of Halliburton, Candler and Sikes[2], and of A. S. Grünbaum and Helen Grünbaum[3], have shown that the extract of the pars posterior of the human pituitary has physiological actions similar to those produced by the same extract from other vertebrate animals.

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 261; *idem.*, 1913, vii, 73.

[2] Halliburton, W. D., J. P. Candler, and A. W. Sikes, *Quart. Journ. Exper. Physiol.*, 1909, ii, 229.

[3] Grünbaum, A. S., and Helen G. Grünbaum, *Journ. Physiol.* (*Proc. Physiol. Soc.*), 1911, xlii, xxviii.

PART III

DISORDERS ASSOCIATED WITH THE PITUITARY AND THEIR TREATMENT

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It was not till the year 1886 that pathological lesions of the pituitary body were recognized and associated with clinical manifestations. In that year Marie[1] described changes in this organ in the disease known as 'acromegaly' (ἄκρος = extremity, and μέγας, μεγάλ- = large). In the following year, possibly independently, Minkowski[2] described in more detail the relationship between acromegaly and lesions of the pituitary. Since then many investigators have not only confirmed this pioneer work and elucidated the finer points in the histopathology of acromegaly, but have extended their observations to other morbid conditions arising from disordered states associated directly or indirectly with the pituitary body.

The earlier investigators were hampered considerably in drawing their conclusions by lack of definite information concerning the anatomy and physiology of the pituitary. Even in the present day there is considerable doubt whether the pituitary body should be considered one organ or two organs; and we shall see that many of the difficulties in regard to the interpretation of pathological phenomena have arisen from this uncertainty concerning the unity or duality of the pituitary.

There is, too, in regard to the normal physiology, another serious obstacle that confronts those who are not fully satisfied with merely recording disjointed facts: I refer to the imperfections in our knowledge concerning the undoubted correlations

[1] Marie, P., *Rev. de Med.*, 1886, vi, 297.
[2] Minkowski, O., *Berl. Klin. Woch.*, 1887, xxiv, 371.

that exist between the pituitary and the other hormonopoietic organs. This lack of comprehension often prevents our knowing whether certain symptoms are due to primary pituitary disease or to associated changes in some other of the organs of internal secretion. This is a difficulty which is likely to trouble us for some time—until far more work has been done on the interrelationships between the internal secretions. Meanwhile, no good can come of attempting to disguise the ill-defined, if not chaotic, state of our acquaintance with the subject. Further, a clear conception of the gaps in our knowledge is necessary before we can identify with certainty the established facts that stand out from the host of other obscurer details with which the subject is burdened.

The recognition, then, of acromegaly as a primary disease of the pituitary body first turned the attention of clinicians to this organ; but it was not until Tamburini[1] showed that there may be two stages—hyperpituitarism and hypopituitarism—associated with acromegaly, and Fröhlich[2] described the condition of *dystrophia adiposogenitalis* (hypopituitarism), that many hitherto little understood and apparently contradictory facts became intelligible.

Much more recently Cushing[3] has described all conditions of perverted pituitary function as 'dyspituitarisms'; and he subdivides these into five clinical or symptomatic groups[4].

From a scientific point of view, as well as for the sake of lucidity, it appears to me better to consider pituitary lesions

[1] Tamburini, A., *Riv. Speriment. di Freniat.*, 1894, xx, 559.

[2] Fröhlich, A., *Wien. Klin. Rundsch.*, 1901, xv, 883.

[3] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[4] The following are the groups described by Cushing:—

"1. Cases of dyspituitarism in which not only the signs indicating distortion "of neighbouring structures, but also the symptoms betraying the effects of altered "glandular activity are outspoken.

"2. Cases in which the neighbourhood manifestations are pronounced, but "the glandular symptoms are absent or inconspicuous.

"3. Cases in which neighbourhood manifestations are absent or inconspicu- "ous, though glandular symptoms are pronounced and unmistakable.

"4. Cases in which obvious distant cerebral lesions are accompanied by symp- "tomatic indications of secondary pituitary involvement.

"5. Cases with a polyglandular syndrome in which the functional disturb- "ances on the part of the hypophysis are merely one, and not a predominant "feature, of a general involvement of the ductless glands."

as primary, and as secondary to disease in the neighbourhood, to general disorders or to derangements of the other organs of internal secretion; and, also, in each case according to whether there is a condition of excess of secretion or deficiency—so far, at any rate, as our knowledge will allow such an estimation.

§ i. PRIMARY LESIONS OF THE PITUITARY

HYPERPITUITARISM[1]

MANY authors do not state whether they consider that in hyperpituitarism only the epithelial elements are concerned; most, however, infer it. In the recent work of Cushing[2] the relative importance of the anterior and posterior lobes is not made sufficiently clear; indeed, this surgeon in the work mentioned contradicts the results of his previously published experimental observations.

A normal condition of hyperhypophysism[3] exists in pregnancy, as already described; and there are, also, fluctuations in the functional activity of the pars anterior, as of other ductless glands, at various periods of life, in accordance with the state of the metabolism in regard to growth, reproduction and decay.

It is still a debated point whether a pathological state of hyperhypophysism is due merely to an increase of secretion, or whether the secretion is also a perverted one. There is considerable evidence in favour of the latter view, and no one has succeeded in producing the symptoms of hyperhypophysism by the administration of hypophysial extracts to the human subject or to animals.

The results of pathological hyperhypophysism (an expression which we will consider admits the possibility of a perverted function) depend on the period of life at which the lesion becomes manifest, and also on the extent of departure from the normal in regard to the secretion.

When there is hyperplasia of the anterior lobe in early life the effect produced depends on the sex of the patient. If the subject be a boy sexual precocity may occur. In the cases on record the evidence is generally incomplete or conflicting as to

[1] 'Hyperpituitarism' implies abnormal activity of the whole organ.

[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[3] 'Hyperhypophysism' implies abnormal activity of the partes anterior and intermedia.

whether the pineal may not have been concerned[1,2]; but the fact that in girls hyperplasia of the pars anterior leads to the manifestations of precocious masculinity—hypertrichosis, a deep voice and the rest—gives point to the view that the pituitary may sometimes be concerned in the way indicated in regard to masculine precocity.

When the onset of hyperhypophysism occurs before the epiphyses have joined, a remarkable growth of the skeleton follows, and gigantism results. Subsequently, the typical signs and symptoms of acromegaly may appear.

If the disease commence late in life when the epiphyses have joined, then, of course, gigantism does not supervene, but certain typical skeletal changes to be described directly are to be seen.

The only specific disease known to be produced by hyperpituitarism is acromegaly, for although gigantism may be associated with this condition, well-marked skeletal development cannot be considered pathological in the absence of acromegaly. It may, in fact, be due merely to adolescent hyperhypophysism, just as one sees in girls hyperthyroidism at puberty—a condition which produces a temporary effect that subsequently subsides.

ACROMEGALY

Incidence of the disease.—Acromegaly occurs more commonly in women than in men, and most often makes its appearance between the 20th and 40th years. It is, in fact, a disease of the reproductive period, and more especially of that immediately following puberty.

In some cases there is a family history of hyperhypophysism, especially in regard to skeletal overgrowth.

Symptoms, signs, and course of acromegaly.—It is very difficult to say what are the prodromal signs—apart from gigantism—if such exist. But among the earliest definite symptoms are slight ocular disturbances, such as photophobia; headache and facial neuralgia, also, are not uncommon, and there is usually, but not always, muscular weakness. At first, the patient may be

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[2] Poynton, F. J., *Proc. Roy. Soc. Med.* (*Neurol. and Ophthalmol. Sects.*), 1913, vi, xviii.

restless, and in men the sexual appetite is sometimes increased[1,2]. A little later, manifestations may occur as the result of the implication of other organs of internal secretion. In men there may be impotence, and in women there is inevitably amenorrhœa and usually sterility. Not infrequently, however, there are periods of abatement in the disease, during which the sexual functions become reestablished. This interesting phenomenon shows us that actual atrophy of the genital organs does not occur —at any rate until late in the disease.

Another very striking train of events in connexion with acromegaly in women is the tendency towards masculinity. The bones become enlarged, the voice deep, the skin coarse and the features heavy. In one case which came under my notice there was considerable hypertrophy of the clitoris, and this caused the patient much mental distress. The metabolism is directed towards calcium retention—an essentially masculine characteristic[3].

The amenorrhœa with which women suffer in acromegaly is probably due to this change to masculinity, and not primarily to hyperpituitarism.

The alterations which take place in the skeleton have been studied by Keith[4], and according to this observer the results produced are due to a hormone secreted by the pars anterior. "It renders," he says, "the osteoblasts hypersensitive to the various stresses which fall on the human skeleton during life. Thus the osteoblasts at the origins and insertions of muscles become increasingly sensitive to the traction of the muscle fibres; the muscular impressions and processes of the skeleton become unduly raised, extended, and emphasized by the formation of new bony matter". Keith reminds us that John Hunter showed that deposition and absorption of bone go hand in hand; and he himself considers that in acromegaly the coordination between growth and absorption is lost.

The patient with acromegaly soon notices that the hands, feet and head are becoming enlarged: larger boots and gloves are required, and if the patient be a man, he will from time to time need larger sizes in hats.

[1] Buday, K., and N. Iansci, *Deutsch. Arch. f. Klin. Med.*, 1898, lx, 385.

[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[3] Bell, W. Blair, *The Sex Complex*, 1916.

[4] Keith, A., *Lancet*, 1911, i, 993.

Fig. 141.

Radiograph of the skull in a case of acromegaly in a man, showing the enlargement of the superciliary ridge, of the frontal sinus and of the sella turcica. (*By Thurstan Holland.*) × ½.

Enlargement of the vault of the skull can be recognized in a radiograph by the increase of bone on the superciliary ridges, and the greater size than normal of the frontal sinuses (fig. 141).

Likewise the enlargement (fig. 142) and often deformation of the sella turcica become noticeable (figs. 143 and 144). In acromegaly there may be thickening of the clinoid processes and

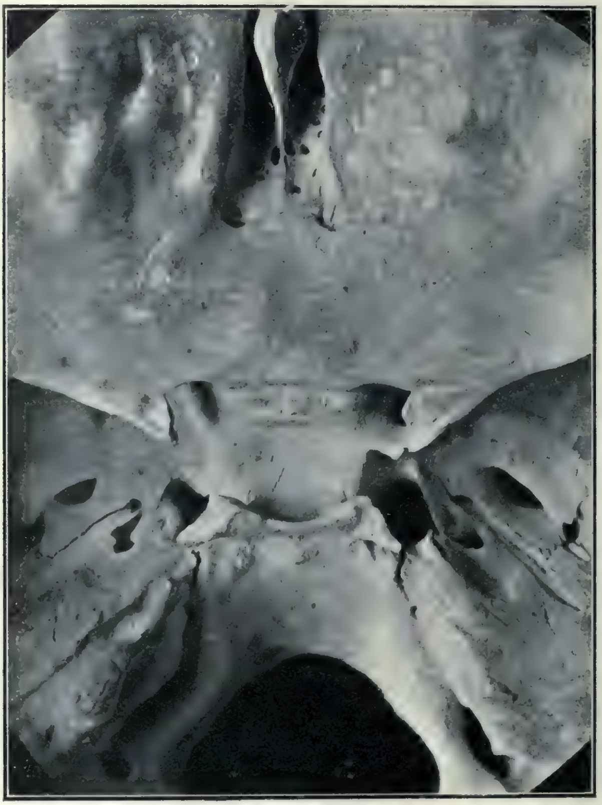


Fig. 142.

Base of the skull in a case of acromegaly, showing the greatly enlarged sella turcica. (*Photograph.*)

× 1/1.

dorsum sellæ, as of the other bones; but eventually there is pressure-atrophy with thinning of the bones and the disappearance of the posterior clinoid process (figs. 141, 143, 144).

According to Johnston[1] there is a form of 'localized acromegaly' in which epilepsy is a common symptom; and this

[1] Johnston, G. C., *Amer. Journ. Roentgenol.*, 1914, i (New Ser.), 172.

FIG. 143.

Radiograph of the skull of a woman suffering with acromegaly, showing enlargement and deformation of the sella turcica. (*By Thurstan Holland.*)

× $\frac{1}{1}$.

FIG. 144.

Radiograph of the skull of a woman suffering with acromegaly, showing the disappearance of the posterior clinoid processes. (*By Thurstan Holland.*)

× $\frac{1}{1}$.

symptom, his radiographic studies lead him to think, is due to the close confinement of the pituitary by the overgrowing clinoid processes and dorsum sellæ.

The changes in the bones of the extremities can, also, easily be recognized in a radiograph: the phalanges become widened

Fig. 145.

Acromegaly in a woman. The features are thickened and heavy and the hands are splayed. (*Photograph.*)

and the terminal bones are tufted at the extremities (fig. 146). These alterations cause the hands to become broad and splayed (fig. 145).

Gradually the face becomes distorted: the malar bones increase in size and the lower jaw so enlarges that it may project beyond the upper (prognathism) (figs. 145 and 147), which is itself often enlarged. There is, however, no increase in the size

FIG. 147.

Profile-view of a woman suffering with acromegaly, showing prognathism. (*Photograph.*)

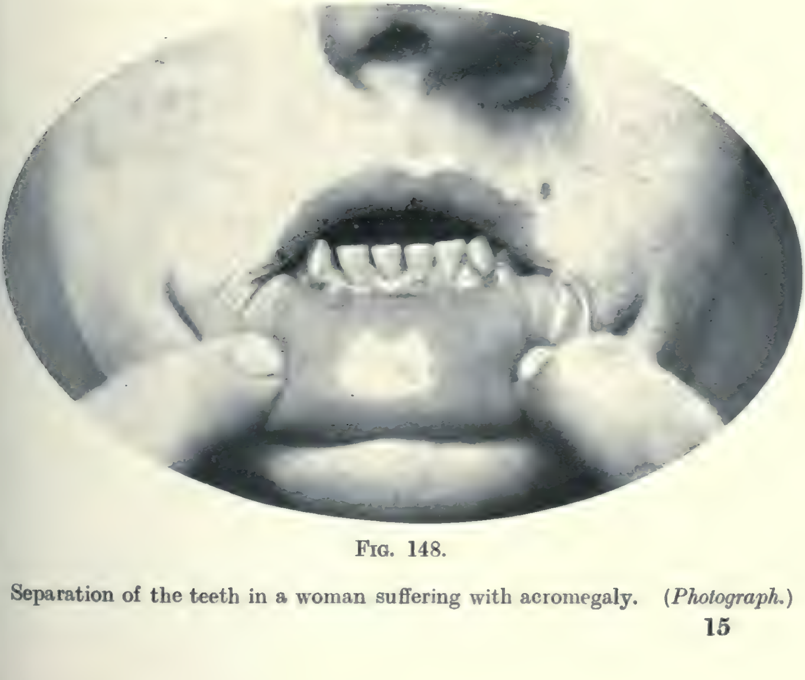


FIG. 148.

Separation of the teeth in a woman suffering with acromegaly. (*Photograph.*)

of the palate. The maxillary expansion involves the whole circumference of the jaws and causes the teeth to become widely separated (fig. 148)—a very constant sign of the disease.

The skin becomes coarse, rough and thick owing to hypertrophy of the papillæ and thickening of the cutis and the subcutaneous tissues, and it may be yellowish or pigmented; the hair and nails become brittle. The nose and ears enlarge and the lower lip becomes bulky and pendulous (fig. 145), as the result of the changes mentioned in the cutaneous and subcutaneous tissues. Likewise there is an increase in the size of the tongue; and the mucous membrane of the nose and pharynx becomes thickened. The enlargement of the tongue may cause the patient to keep the mouth always open, and the thickening of the nasal mucosa gives rise to discomfort and difficulty of breathing, and even to deafness from involvement of the Eustachian tubes. The patient often suffers with polyuria, and glycosuria, the result of hyperglycaemia, is sometimes present.

Unless the disease become arrested—as not infrequently happens—various other symptoms soon make their appearance: the patient complains of *tinnitus aurium*, and invariably of the severity of the 'pituitary headache' which results from pressure in the pituitary fossa, of giddiness, unsteady gait and occasionally of epileptiform seizures; and there is usually progressive lassitude and torpidity, although sometimes the psychical functions remain undisturbed until an advanced stage of the disease. Vomiting due to intracranial pressure is rare, but may occur.

Simultaneously with the symptoms just described, or later, the patient complains of serious disturbances of vision. On examination, various degrees of divergence from the normal, according to the extent of the intracranial injury to the optic tracts, are found. Bitemporal hemianopia is usually present early in the disease (fig. 149), but is often undiscovered at first by the patient, owing to the fact that colour-vision disappears before the white field (fig. 150, A). Sometimes there is diplopia; and even external strabismus from injury of the third nerve is not uncommon. Eventually the fields of vision may become extremely restricted (fig. 150, B), and finally blindness may supervene from atrophy of the optic nerves. Extensive involvement, however, of the optic tracts and of the oculomotor nerve is,

according to Cushing[1], uncommon in acromegaly. Sometimes there is exophthalmos.

This train of events, short in the description, takes long in the development. Patients suffering with acromegaly live for many years in a condition of hyperhypophysism, but most of them drift finally into the condition of hypohypophysism which I shall describe presently, and this occasionally after a period of apparent quiescence in the disease. In very rare cases when acromegaly has been due to a functionating malignant tumour of the anterior lobe the disease runs a rapidly fatal course[2].

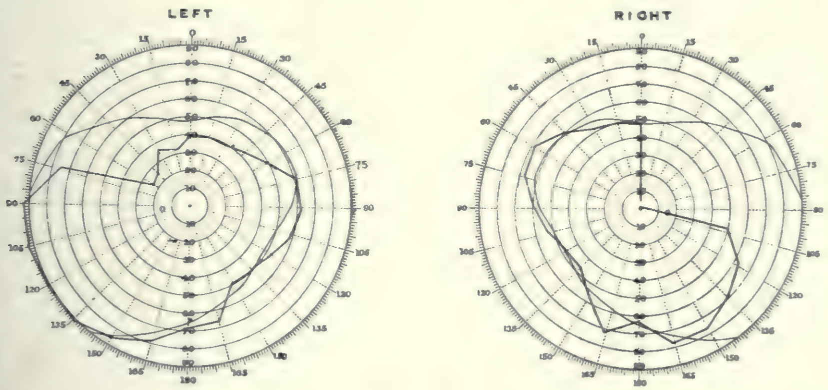


Fig. 149.

Restricted white fields of vision in a case of acromegaly. (*By T. H. Bickerton.*)

As we have seen, during pregnancy the activity of the anterior lobe is normally increased, and, as a result, minor and temporary symptoms of acromegaly may occasionally occur, especially thickening of the subcutaneous tissues. Marek[3] has reported a case in which acromegaly, with glycosuria, prognathism and some of the other symptoms of the disease, commenced during pregnancy and disappeared during the puerperium.

The metabolism in acromegaly.—Observations concerning the metabolic disturbances in acromegaly are so conflicting that it is probable that many of the abnormalities found depend not

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.
[2] Fischer, B., *Hypophysis, Akromegalie und Fettsucht*, Wiesbaden, 1910.
[3] Marek, R., *Zentralbl. f. Gynak.*, 1911, xxxv, 1612.

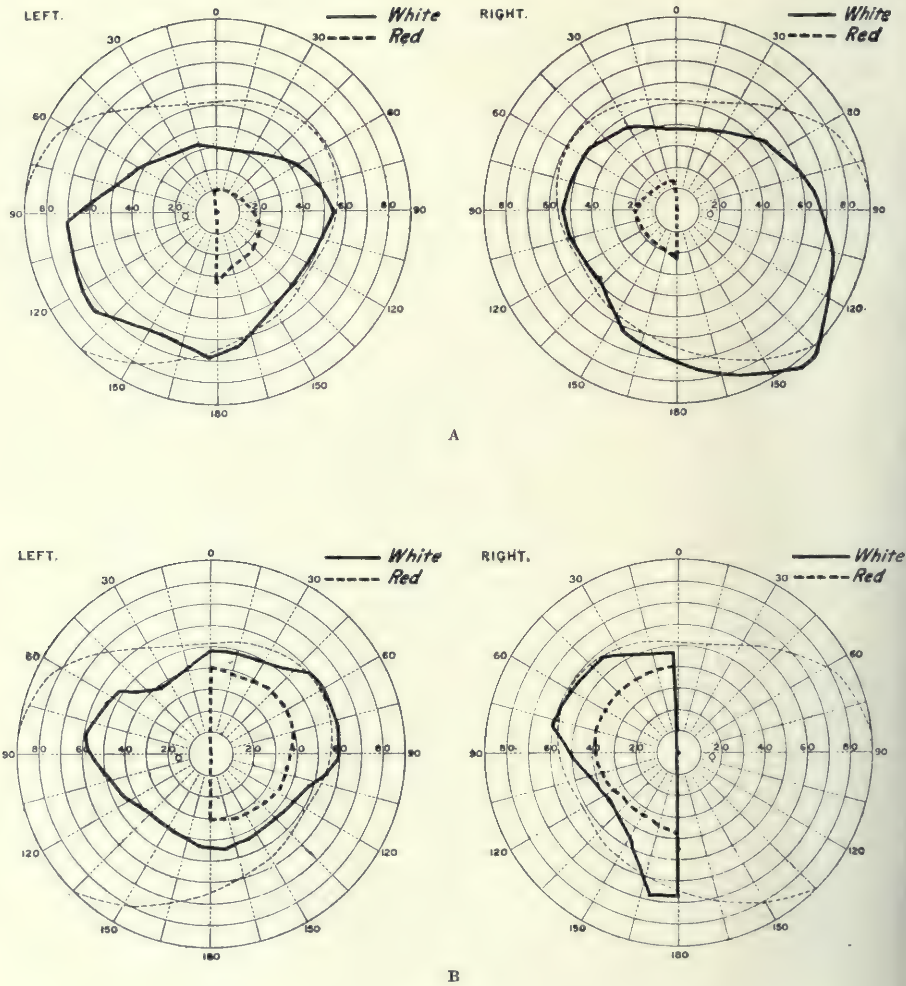


Fig. 150.

Fields of vision (colour and white) in a case of acromegaly. A, on December 18th, 1911, when the colour-fields were greatly restricted, and the white fields only slightly. B, on February 17th, 1913, when the white fields were much limited and the colour-fields less than previously. (*Doyne.*)

only on hypophysial disease, but also on a pluriglandular syndrome.

Franchini[1], and Franchini and Giglioli[2] investigated several cases of acromegaly and concluded that in the active stages of the disease there is an excessive excretion of nitrogen and phosphorus, and a considerable retention of calcium and magnesium. These observers state that the metabolism of chlorine, sodium, and potassium is not appreciably altered. Moraczewski[3] and others have found an abnormal retention of calcium and phosphorus.

TABLE XI.

N. H. FEMALE, ÆT. 30 YEARS. CASE OF ACROMEGALY. EXAMINATION OF URINE.

Date.	Quantity per diem.	Reaction.	Sp. Gr.	Acetone.	Diacetic acid.	Albumen.	Sugar.	Total Nitrogen.	T. Nitrogen as Urea.	Ammonia Nitrogen.	A.N. as % of T.N.	NaCl.	P_2O_5.	Calcium.
	c.c.							grms.	grms.	grms.	%	grms.	grms.	%
28.1.15		acid	1016	—	—	—	—	0·78	1·69	0·064	8·1	0·34	0·17	0·016
29.1.15		acid	1010	—	—	—		0·49	1·13	0·039	7·3	0·38	0·188	0·013
30.1.15		acid	1015	—	—	—		0·714		0·071	0·10	0·4	0·288	0·0145
1.2.15		acid	1015	—	—	—		0·77		0·059	7·7	0·3	0·318	0·0017
2.2.15		acid	1012				—	0·63		0·05	8·0	0·32	0·212	0·0095
3.2.15[4]	513	neutral	1012				—	0·448		0·04	9·0	0·45	0·161	0·0052
12.2.15	1311	acid	1013				—	0·462	1·75	0·067	14·5	0·37	0·26	0·0004
13.2.15	1625	acid	1012				—	0·742	1·22	0·061	8·3	0·3	0·15	0·032
15.2.15	1083	acid	1015				—	0·84	1·75	0·061	7·3	0·35	0·34	0·0227
16.2.15		acid	1013				—	0·644	1·41	0·05	7·8	0·41	0·22	0·0088
17.2.15	1311	acid	1012					0·826	1·75	0·05	6·1	0·4	0·24	0·0005
18.2.15	1254	acid	1014					0·812	1·72	0·047	5·8	0·3	0·33	0·001
19.2.15	1311	acid	1015					0·700	1·41	0·049	7·0	0·25	0·24	0·001
20.2.15	1311	acid	1011			—	—	0·559	1·19			0·35	0·23	0·003
22.2.15	1454	acid	1020			—	—	0·729	1·55	0·07	9·6	0·5	0·18	0·0015
23.2.15	1340	acid	1015			—	—	0·491	1·061	0·05	10·0	0·6	0·17	0·0015
24.2.15	1653	acid	1010			—	—	0·43	1·0	0·04	8·6	0·26	0·21	0·0002

I have examined the urinary excretions of two cases of acromegaly with the patients on a full mixed diet. Tables XI and XII show the results obtained.

[1] Franchini, G., *Riv. Speriment. di Freniat*, 1907, xxxiii, 888; and *Berl. Klin. Woch.*, 1908, xlv, 1636.

[2] Franchini, G., and G. J. Giglioli, *Nouvelle Icon. de la Salpêtrière*, 1908, xxi, 325.

[3] Moraczewski, W. D. von, *Zeit. f. Klin. Med.*, 1901, xliii, 336.

[4] Decompression operation: February 3, 1915. Calcium index in blood, 1·05.
February 16, 1915. Calcium index in blood, 0·54.

It will be seen that there is no definite abnormality to be discovered, except in regard to the calcium metabolism. The excretion of this substance was very variable and below normal except on a few occasions, when large quantities were excreted.

TABLE XII.

G. J. MALE, ÆT. 27 YEARS. CASE OF ACROMEGALY. EXAMINATION OF URINE.

Date.	Quantity per diem.	Reaction.	Sp. Gr.	Acetone.	Diacetic acid.	Albumen.	Sugar.	Total Nitrogen.	T. Nitrogen as Urea.	Ammonia Nitrogen.	A.N. as % of T.N.	NaCl.	P_2O_5.	Calcium.
	c.c.							grms.	grms.	grms.	%	grms.	grms.	%
17.2.15[1]		acid	1025			—	—	1·62	3·45			0·5	0·46	0·0061
18.2.15		acid	1011			—	—	0·644	1·37	0·072	11·3	0·4	0·16	0·0064
19.2.15	1197	acid	1006			—	—	0·98	2·1	0·056	5·6	0·08	0·088	0·0006
20.2.15	1223	acid	1019			—	—	1·75	3·72			0·34	0·26	0·0005
22.2.15	1254	acid	1019			—	—	1·72	3·66	1·11	6·4	0·55	0·209	0·0044
23.2.15	1484	acid	1012			—	—	1·12	2·33	0·055	5·0	0·23	0·109	0·035
24.2.15	1140	acid	1012			—	—	1·08	2·32	0·072	6·6	0·2	0·259	0·004
25.2.15	1111	acid	1017			—	—	0·99	2·1	0·106	10·7	0·349	0·289	0·01
26.2.18	1254	acid	1015			—	—	1·11	2·54	1·12	0·606	0·24	0·22	0·0022
27.2.15	1340	acid	1011			—	—	1·3	2·74	0·084	6·4	0·17	1·4	0·013
2.3.15	1454	acid	1010			—	—	0·63	1·3	0·53	8·3	0·29	0·094	0·0004

The pathology of acromegaly.—Before describing the more exact observations which have been made concerning the pathological histology, I must refer to an interesting theory, recently revived by Keith[2], namely, that acromegaly may represent an atavistic tendency, since the acromegalic skull resembles in its prognathism the skull of primitive Man and of the higher apes. I am not aware that any histological evidence has been adduced to support this theory, although I have found that there is normally a greater degree of chromophobia in the pars anterior in some of the lower orders of mammals, such as the rodents, than in the higher.

The histological pathology of acromegaly has been carefully investigated by Benda[3], Fischer[4], Cushing[5] and many others.

[1] Calcium index in blood, 0·4.

[2] Keith, A., *Lancet*, 1911, i, 993.

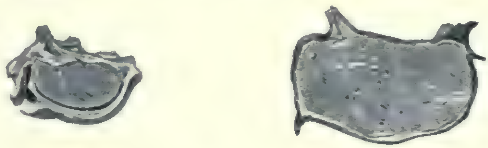
[3] Benda, C., *Berl. Klin. Woch.*, 1900, xxxvii, 1005; *Handbuch d. Pathol. Anat. d. Nervensystem*, 1904, ii, 1418.

[4] Fischer, B., *Hypophysis, Akromegalie und Fettsucht*, Wiesbaden, 1910.

[5] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

The disease is almost always accompanied by considerable hypertrophy of the pars anterior (fig. 151), and an enlargement of the sella turcica which can be demonstrated by X-rays. Occasionally, however, no definite enlargement has been found[1,2].

Benda has shown that the histological changes in the anterior lobe may consist of so considerable an increase of the eosinophil cells that the whole gland appears to consist of this one type of cell. He has also found that these cells often assume an adenomatous arrangement. Benda could find no record in the literature of any tumour other than an adenoma—presumably innocent or malignant—being associated with acromegaly. Benda[3], Lowenstein[4], Fischer[5], and Cushing[6] believe that many cases of hyperplasia have been taken for sarcomata and peritheliomata, owing to the rapidity of proliferation and the difficulty of recognizing the different stages in the development of the cells.



A B

FIG. 151.

The normal pituitary (A) shown for comparison in regard to size with the pituitary in a case of acromegaly (B). (*From a photograph kindly lent by the Medical Superintendent of Whittingham Asylum.*)

$\times \frac{1}{1}$.

Cagnetto[7] has reported a case of sarcoma of the pituitary in a girl aged 9, which was not associated with acromegaly; and Rennie[8] a case of endothelioma in a boy, 16 years of age, in which there was some degree of infantilism. It is probable that usually in these circumstances the secretory cells of the pituitary are destroyed. Fischer[5], moreover, states that tuberculous and

[1] Lewis, D., *Bull. Johns Hopk. Hosp.*, 1905, xvi, 157.

[2] Linsmayer, L., *Wien. Klin. Woch.*, 1894, vii, 294.

[3] Benda, C., *Berl. Klin. Woch.*, 1900, xxxvii, 1005; *Handbuch d. Pathol. Anat. d. Nervensystem,* 1904, ii, 1418.

[4] Lowenstein, C., *Virchow's Arch.*, 1907, clxxxviii, 44.

[5] Fischer, B., *Hypophysis, Akromegalie und Fettsucht*, Wiesbaden, 1910.

[6] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[7] Cagnetto, G., *Virchow's Arch.*, 1907, clxxxviii, 197.

[8] Rennie, G. E., *Brit. Med. Journ.*, 1912, i, 1355.

syphilitic lesions of the hypophysis do not cause acromegaly. In these circumstances, also, the lesions would be destructive and not hyperplastic in character.

Cagnetto[1], Sternberg[2] and Fischer[3] believe that adenocarcinoma of the pars anterior may produce acromegalic symptoms. Fischer in discussing the question remarks that there is great individuality with regard to the metastases of various malignant tumours: sometimes metastases will produce secretion, and at other times they will not. It is for this reason he believes that some malignant tumours of the pituitary cause acromegaly, while others do not. I shall refer to this subject later (p. 269).

Furnivall[4] collected results of post-mortem examinations performed upon 49 cases of acromegaly by many different pathologists. Of this number 11 were stated to be due to sarcomata, 7 to simple hypertrophy, 6 to adenomata and 9 to 'tumours' of the hypophysis. Rolleston, also, has recorded a case of sarcoma of the pituitary, which invaded the brain and petrous bone. It is probable, however, that hyperplasia of the hypophysis has frequently been mistaken for sarcoma.

It has often been argued that some of the symptoms of acromegaly may be due to interference with the function of the posterior lobe. This is probably true in regard to glycosuria which, when present, may be secondary either to injury (by compression) of the pars posterior, or to hyperplasia of the pars intermedia. Nevertheless, in this connexion it is important to remember that acromegaly has been known to exist without enlargement of the hypophysis[5,6]. Such a condition is probably comparable with cases of hyperthyroidism, without enlargement of the thyroid.

In discussing the pathology of acromegaly Cushing[7] reports cases diagnosed clinically as hyperhypophysism, which on post-mortem examination revealed in most instances a 'strumous' condition—that is, hyperplasia either of the eosinophil or more rarely of the chromophobe cells. In a very few there was cystic or necrotic degeneration in the pars anterior. Fischer[3]

[1] Cagnetto, G., *Virchow's Arch.*, 1907, clxxxviii, 197.

[2] Sternberg, M., *Zeit. f. Klin. Med.*, 1895, xxvii, 86.

[3] Fischer, B., *Hypophysis, Akromegalie und Fettsucht*, Wiesbaden, 1910.

[4] Furnivall, P., *Trans. Path. Soc.*, 1898, xlix, 204.

[5] Lewis, D., *Bull. Johns Hopk. Hosp.*, 1905, xvi, 157.

[6] Linsmayer, L., *Wien. Klin. Woch.*, 1894, vii, 294.

[7] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

asserts that eosinophil adenoma is the hall-mark of acromegaly.

It appears, therefore, that the symptoms of the disease known as acromegaly are primarily dependent on an excessive secretion of the eosinophil or the active chromophobe cells of the anterior lobe (fig. 152). This is in keeping with the explanation already given of the secretory functions of the cells of the pars anterior.

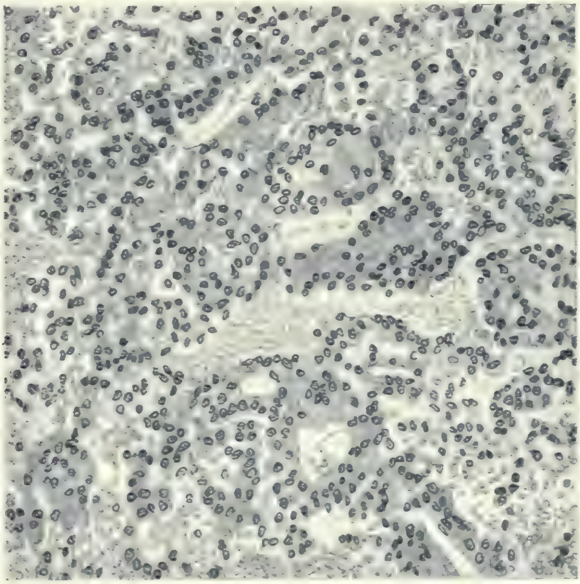


FIG. 152.

Section of a portion of the pars anterior removed at operation (*by W. Thelwall Thomas*) from a case of acromegaly, showing an adenomatous arrangement of chromophobe cells. There is much blood scattered through the section—probably the result of surgical interference.

× 150.

Although in these circumstances there is always at first a condition of hyperplasia present in the pars anterior, it is probable that the main features of acromegaly exist for some time after the anterior lobe has ceased to be excessively active. Further, it has rightly been emphasized by Cushing that hypopituitarism very frequently succeeds hyperpituitarism, and that it is not uncommon to find in this later stage a cystic or necrotic change present in the anterior lobe.

Before leaving the discussion of the pathology of acromegaly and the question of the actual situation of the lesion in the pituitary body, it is necessary briefly to refer to the interesting fact that acromegaly may be caused by hyperplasia in an accessory anterior lobe; that is to say, hyperplasia may occur in a congenital inclusion of the hypophysis in the track of the craniopharyngeal canal through the sphenoid bone. These inclusions of a portion of Rathke's pouch are probably not rare, but only a few cases are known in which acromegaly has arisen from such rests. Erdheim[1] has recorded such a case. He found an eosinophil hypophysial tumour, extending into the sphenoidal cells below the sella turcica, which had been associated with the symptoms of acromegaly. The pituitary body proper was quite normal.

The following question now arises: How far are pathological lesions in the pituitary responsible for the clinical manifestations associated with acromegaly?

Tandler and Grosz[2] considered that hyperplasia and eventually hypoplasia in the pituitary were secondary to primary genital atrophy. This assumption was partly based on experimental evidence; but it in no way accords with the clinical facts, for genital hypoplasia follows, rather than precedes, the onset of acromegaly, and undergoes remissions when improvements occur in the course of the disease.

In most cases there is no doubt that while in this disease the primary pathological lesion is in the epithelial portions of the pituitary and most of the clinical manifestations are the result thereof, yet in their entirety the clinical phenomena form a pluriglandular syndrome. This, indeed, is the only explanation that can be offered in some anomalous cases.

Many recent observers have recognized changes in the other hormonopoietic organs in acromegaly; but if we except tentative discussions by Biedl[3] and Cushing[4], and the work of Claude and Gougerot[5] on somewhat similar lines, it does not appear to have been seriously put forward that primary disease of an organ of

[1] Erdheim, J., *Beitr. z. Pathol. Anat. u. z. Allg. Pathol.*, 1909, xlvi, 233.

[2] Tandler, J., and S. Grosz, *Wien. Klin. Woch.*, 1907, xx, 1596.

[3] Biedl, A., *Innere Sekretion*, 2nd ed., 1913.

[4] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[5] Claude, H., and H. Gougerot, *Journ. de Physiol. et de Pathol. Gen.*, 1908, x, 469 and 505.

internal secretion does not produce symptoms entirely dependent upon that lesion, but rather upon a pluriglandular involvement. It is, for example, not impossible that hyperthyroidism—apparently a pathological entity—is dependent partly on the withdrawal of the restraining influence of other internal secretions.

The way for this point of view has been prepared by our consideration of the physiological interrelations between the pituitary and the other organs of internal secretion; but in order to view the whole subject more completely I shall first consider the pathological condition known as 'hypopituitarism'.

Incidence and symptoms.—It is possible that hypopituitarism may exist as a congenital lesion, but such a state of affairs is difficult to determine, for it is not until the child is growing up that the signs of this lesion become recognizable.

Hypopituitarism occurring before puberty gives rise to three distinct conditions: (*a*) infantilism somatic and sexual, without adiposity (Lorain type); (*b*) stunted growth with sexual infantilism and adiposity; (*c*) overgrowth with some adiposity and genital inactivity.

Levi[1] was probably the first to direct attention to infantilism (Lorain type) due to pituitary lesions.

This type of case is attributed by Cushing[2] and others to insufficiency in the secretion of the pars anterior; and in his case (iv) there was an enlargement of the sella turcica.

I have seen a case in which a girl at the age of 18 years resembled a child of 10 years of age (fig. 153), and in whom there was a shallow sella turcica (fig. 154).

Rennie[3], also, has recorded an interesting case of this type of infantilism in a boy suffering with an endothelioma of the pituitary.

It seems probable that in those cases in which the sella turcica is small the condition has existed *ab initio;* while in those in which the sella is distorted and large there has been some postnatal and preadolescent destruction of the pars anterior without injury to the pars posterior. It is probable, also, that when there is a preadolescent lesion of the pituitary producing adiposity, stunted growth and sexual infantilism, the whole organ is affected.

Since the condition of *dystrophia adiposogenitalis* was first described by Fröhlich[4] in the case of a boy, 14 years of age, a

[1] Levi, E., *Nouv. Icon. de la Salpêtrière*, 1908, xxi, 297 and 421.

[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[3] Rennie, G. E., *Brit. Med. Journ.*, 1912, i, 1355.

[4] Fröhlich, A., *Wien. Klin. Rundsch.*, 1901, xv, 883.

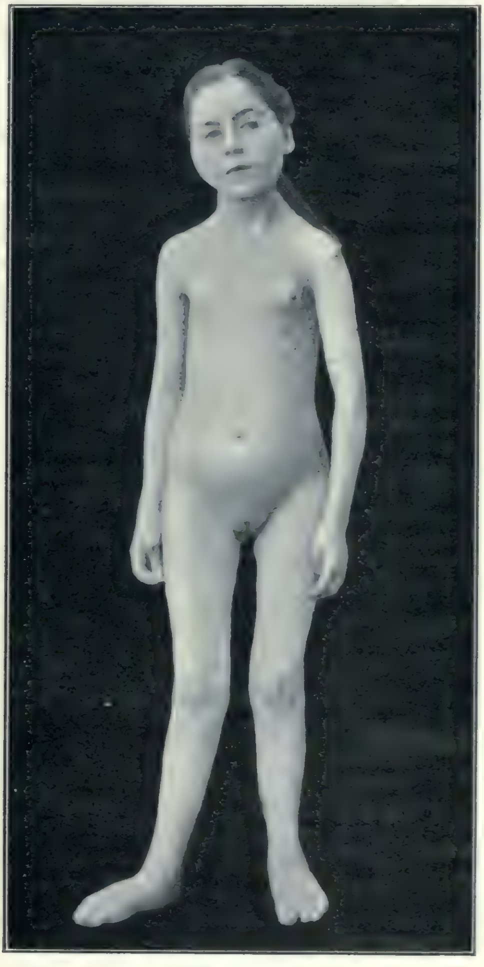


Fig. 153.

Photograph of a girl, aged 18 years, showing general infantilism due to under-development of the pituitary. The patient measured 4 ft. 3 ins. in height and weighed 4 stones 3 lbs.

number of cases of this state of affairs is on record[1,2]—so many that it is impossible to give all the references.

One of the most interesting cases is that of Madelung[3] in which a girl 9 years of age was shot with a rifle-bullet which lodged in the sella turcica. The child developed the typical symptoms of this syndrome, but these were not recognized as such when the case was reported.

Most of the cases, however, have been due to neoplasms or cystic formations in the pars anterior.

FIG. 154.

Radiograph of the sella turcica in the case of ateliosis illustrated in figure 146. (*By Thurstan Holland.*)

$\times \frac{1}{1}$.

The syndrome, *dystrophia adiposogenitalis*, is easily recognized (fig. 155). I shall discuss it in detail presently; but one point must be mentioned here. In boys the skeleton tends to develop on feminine lines, for the bones are light and the extremities tapering.

The third group of preadolescent cases of hypopituitarism, in which there is some skeletal overgrowth with adiposity and genital inactivity, has been described by Neurath[4] and Cushing[1]. Cushing interprets the phenomena seen as being dependent on

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[2] Special discussion, *Proc. Roy. Soc. Med.* (*Neurol. and Ophthalmol. Sects.*), 1913, vi, 1.

[3] Madelung, O., *Virhandl. d. Deutsch. Gesellsch. f. Chir.*, 1904, xxxiii, 164.

[4] Neurath, R., *Wien. Klin. Woch.*, 1911, xxiv, 43.

excessive secretion from the pars anterior with diminished pars posterior secretion. But this certainly does not explain the genital infantilism in the case of males. Neurath, however, considers it possible that the whole train of symptoms is due to primary lesions in the gonads producing a condition of resembling eunuchism. But neither of these explanations quite accounts for the features of the following case.

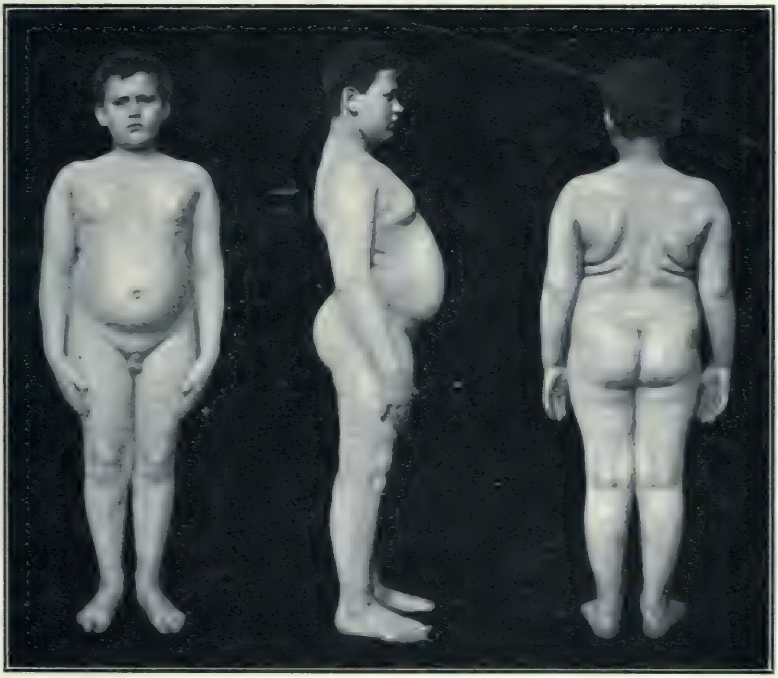


Fig. 155.

Three views of a boy, aged 16 years, suffering with *dystrophia adiposogenitalis.* He measured 4 ft. 6 ins. in height and weighed 7 st. 9 lbs. There was a carbohydrate-tolerance of over 300 grammes of sugar. (*Photograph.*) (*F. E. Batten.*)

This patient came under observation at the age of 18½ years, being referred to me by her father who is a doctor. Her only complaint was that she had not menstruated. On examination the uterus was found to be infantile—rudimentary, I thought at the time.

A radiograph of the sella turcica showed this fossa to be remarkably small (fig. 156). When first seen the patient was a bright, handsome, finely developed girl measuring 5 feet 8½

inches in height, and weighing 11 stones 2 pounds. The carbohydrate-tolerance was over 350 grammes of dextrose—that is to say, no sugar appeared in the urine after this amount had been consumed, and it was impossible for the patient to take more.

Two years later her father wrote to say that she weighed 15 stones 4 pounds in spite of the administration of whole-gland pituitary extract. After that time the administration of pituitary extract was discontinued.

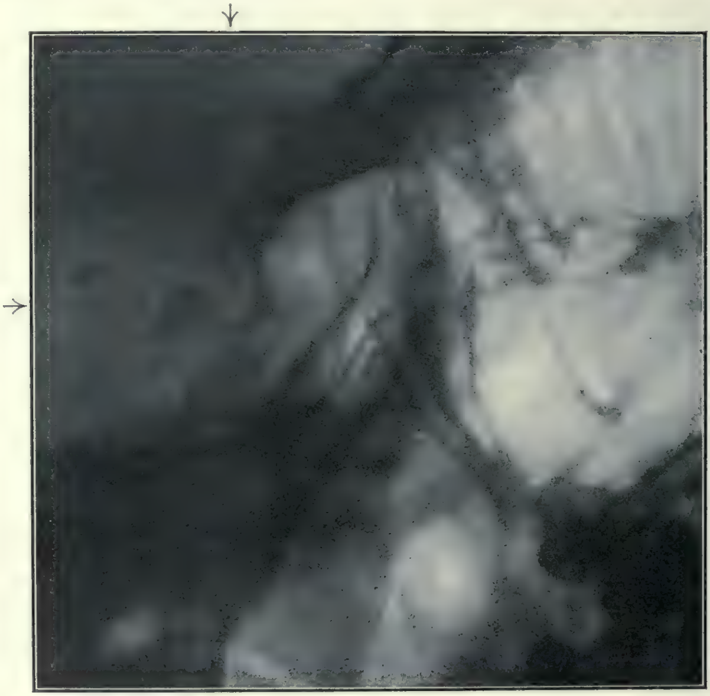


Fig. 156.

Radiograph of the human sella turcica in a case of underdevelopment of the pituitary associated with an infantile uterus. (*By Thurstan Holland.*)

× $\frac{1}{1}$.

Recently, at the age of 23 years, the patient has commenced menstruating regularly. It is this last fact which almost places the case in a category of its own.

After puberty there may be, as in hyperpituitarism, many stages and phases of hypopituitarism; but, as is so frequently the case in newly described conditions, only the most pronounced

types are generally recognized, while the less severe lesions with slight clinical manifestations escape adequate recognition.

The milder forms of hypopituitarism are undoubtedly much commoner than is generally supposed. The patients are usually of the female sex between 25 and 35 years of age. The most prominent symptoms are increasing obesity, lassitude and amenorrhœa. Advice is usually sought for the menstrual suppression. At first the amenorrhœa alternates with irregular and scanty menstruation, and finally this function ceases.

Most text-books of gynæcology describe obesity as a primary cause of amenorrhœa and sterility. That it may be is probable[1]; but it appears likely that in many cases the obesity is really due to pituitary insufficiency. I have seen atrophy of the uterus from this cause in a woman of 36 years of age. Up to 30 years of age her menses had been regular.

In the adult, as in the child, the more serious states of hypopituitarism—produced by cysts, neoplasms or traumatic lesions—form the definite syndrome *dystrophia adiposogenitalis*. In this condition the subject becomes obese; and the male assumes a feminine configuration (feminine type) (fig. 157). In the female menstruation ceases; in the male there is impotence; and the genital organs of both sexes eventually atrophy. The blood-pressure is low and the temperature subnormal. There is, also, so great an increase in the carbohydrate-tolerance with hypoglycaemia, that the ingestion of more than 500 grammes of dextrose may be required to produce glycosuria. The sugar-tolerance may be reduced and the blood-pressure raised by the injection of an extract of the posterior lobe, while the temperature may be elevated by anterior lobe extract (' thermic reaction ' of Cushing).

FIG. 157.

Case of *dystrophia adiposogenitalis* in a man, showing a tendency to feminine contour (*typus feminina*). (*Photograph.*) (*Grainger Stewart and Parsons.*)

In the more severe and progressive types of the disease the

[1] Marshall, F. H. A., *Sci. Progress*, 1908, ii, 369.

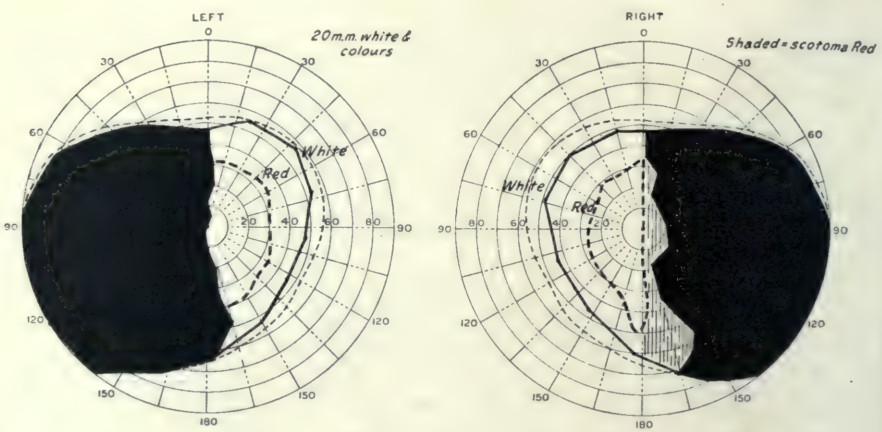


FIG. 158.

Fields of vision in a case of *dystrophia adiposogenitalis,* showing bitemporal hemianopia, and disappearance of the colour-fields before the white. (*Bishop Harman.*)

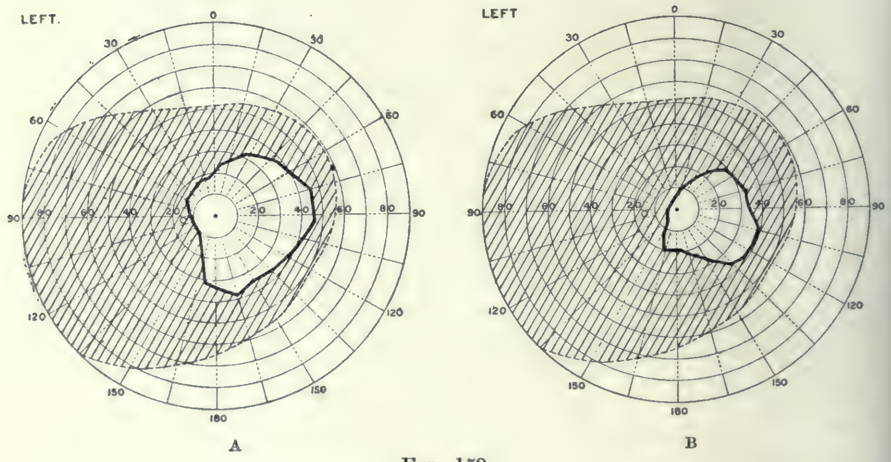


FIG. 159.

Left fields of vision in the case of *dystrophia adiposogenitalis* shown in figure 157, showing gradual progression towards blindness: A, on May 10, 1911; B, on Feb. 12, 1913. (*Grainger Stewart and Parsons.*)

increasing size of the tumour raises the intracranial tension, causing severe headaches, and by injury to the optic tract gives rise to hemianopia—colour-vision disappearing before the white field (fig. 158)—sometimes diplopia, and eventually almost complete blindness (fig. 159). In these circumstances the sella turcica is usually greatly enlarged, and often the posterior clinoid processes are completely eroded (fig. 160). The deformation of the sella is usually greater in *dystrophia adiposogenitalis* than in acromegaly. Vomiting is very rare in these cases.

Fig. 160.

Radiograph of the sella turcica in a case of *dystrophia adiposogenitalis*, showing disappearance of the posterior clinoid processes. The fields of vision of this case are shown in figure 158. (*Bishop Harman.*)

Psychical disturbances may be present as the result of pressure on the frontal lobes; and a specific hypophysial psychosis, due, it is supposed, to perverted pituitary secretion, has been described. The subjects may, however, show all degrees of cerebral disturbance from a torpidity or irritability to advanced forms of epilepsy and insanity.

The relationship of epileptiform seizures to lesions producing hypopituitarism has been studied by Cushing[1].

There appears to be no doubt that, with a pituitary lesion

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

extending upwards into the interpeduncular region, pressure on, or irritation of, the uncinate gyrus may be produced. In these circumstances attacks of loss of memory, or even 'fits' preceded by gustatory or olfactory phenomena, occur. These manifestations, with general epileptiform seizures, appear occasionally to follow pituitary insufficiency apart from pressure on the gyrus, and are probably due to increased cortical irritability.

The skin of patients with hypopituitarism differs from that of patients suffering with acromegaly: in the former condition the integument is soft and smooth, the hair tends to fall out, and, unless the condition be a sequel to acromegaly, the extremities are usually delicate and tapering.

The pathology of hypopituitarism.—As we have seen in certain preadolescent types, the lesion of the pituitary may be congenital; but of this we have no certain knowledge.

Until quite recently it had been accepted by nearly all who have inquired into the subject that hypopituitarism is, strictly speaking, hypohypophysism—that is to say, insufficiency of the partes anterior and intermedia. In order to discuss this question we shall be obliged to reconsider the relative positions occupied by the anterior and posterior lobes, including the pars intermedia.

The experimental work of Paulesco[1], of Cushing[2] and his colleagues, and of Biedl[3] appeared to place beyond all doubt the fact, as emphasized by them in their respective publications, that in dogs *dystrophia adiposogenitalis* is always produced by partial extirpation of the anterior lobe, and that removal of the posterior lobe causes no symptoms. Yet we find that Cushing who has done the most experimental work on this subject, and was apparently certain of his results and conclusions, in his clinical exposition[4] states that the condition of hypopituitarism is due to posterior lobe insufficiency. This view has also been advanced by Fischer[5], apparently on pathological grounds.

The reason why Cushing changed his views appears to have been partly because of post-mortem findings, and partly because

[1] Paulesco, N. C., *L'hypophyse du cerveau*, Paris, 1908.

[2] Crowe, S. J., H. Cushing, and J. Homans, *Bull. Johns Hopk. Hosp.*, 1910, xxi, 127.

[3] Biedl, A., *Innere Sekretion*, 2nd ed., 1913.

[4] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[5] Fischer, B., *Hypophysis, Akromegalie und Fettsucht*, Wiesbaden, 1910.

injections of the extract of the posterior lobe lessen some of the symptoms associated with hypopituitarism, such as the carbohydrate-tolerance and the low blood-pressure. On the other hand, he himself pointed out that the subnormal temperature found with hypopituitarism is raised by extract of the anterior lobe ('thermic reaction'), and not by infundibulin. Apart from the effects produced by the extract of the posterior lobe in hypopituitarism, Cushing adduces other clinical evidence which, he considers, confirms his latest conclusions. He states that an internal hydrocephalus may produce insufficiency of the secretion ot the posterior lobe, and at the same time "may apparently either stimulate or inhibit the anterior lobe" [1]. But the fact that the pars nervosa of the pituitary in man is not hollow, as it is in some of the lower animals, and cannot, therefore, be distended by intraventricular tension appears to have been overlooked by Cushing. Any pressure that may be produced by hydrocephalus in Man must affect equally both lobes.

This observer, therefore, introduces a fresh syndrome: namely, a condition of adiposity with sexual precocity or excitation. Further, this syndrome may be associated, he says, with skeletal undergrowth or overgrowth. Cases are cited, it must be admitted, from his exceptional experience to illustrate these phenomena; but whether a correct interpretation has been placed on them is open to argument.

With regard to Cushing's experiments and those of Biedl, I have demonstrated that it is possible to remove large or small quantities of the anterior lobe and so to bring about insufficiency in this structure, as is shown by the genital atrophy which subsequently occurs, without in any single case producing the syndrome *dystrophia adiposogenitalis* by this procedure. Further, it has been proved that removal of the whole or a portion of the posterior lobe causes neither genital atrophy nor carbohydrate-tolerance. The only way in which I was able to produce *dystrophia adiposogenitalis* was by separating or clamping the stalk.

These results, read in conjunction with the foregoing views of Cushing, serve to illustrate the uncertainty of our knowledge, or at any rate the conflicting nature of the experimental evidence at our disposal for interpretation into the terms

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

of clinical phenomena. Fischer[1], without any experimental data of his own to support him and arguing from a pathological standpoint, asserts that *dystrophia adiposogenitalis* is due to lesions of the posterior lobe. My experimental results show that interference with the stalk is the only lesion which gives rise to this condition.

Erdheim[2] has shown that not infrequently in *dystrophia adiposogenitalis* aggregations of squamous or columnar epithelium are found in the neighbourhood of the cleft. These are either embryonic rests or metaplasias, and from them growths and cysts may arise. Seven cases have been described by Erdheim, and similar tumours have been recorded by others. Cushing[3], in an interesting discussion of the subject, mentions a case of a tumour arising in the upper part of the cleft, and he illustrates the histological appearances which resemble those of thyroid tissue. It is doubtful, however, whether large aggregations of colloid-containing acini in the pars intermedia of the human subject can be considered neoplastic. I have seen this condition well marked in pregnancy, and in other conditions. Possibly this state of affairs is pathological in so far as the amount of colloid and the extent of the acinous formation of the cells are concerned, but it does not usually constitute neoplasia.

When there is a definite tumour in the neighbourhood it may cause compression of the pituitary and interfere with its function to such an extent as to produce *dystrophia adiposogenitalis*. There are many cases of this character on record.

On the other hand, it is, of course, obvious that extreme hyperplasia and other causes of enlargement of the anterior lobe will produce pressure on the posterior. Yet all the evidence in our possession seems to point to the fact that insufficiency of the pars posterior is not primarily the cause of *dystrophia adiposogenitalis*, especially as the whole of this part of the pituitary can be removed without causing symptoms. It seems to me more probable that in these circumstances the syndrome may be caused by the pressure produced by enlargement of the pars anterior on the cells themselves, and on the blood-sinuses.

[1] Fischer, B., *Hypophysis, Akromegalie und Fettsucht*, Wiesbaden, 1910.

[2] Erdheim, J., *Sitz. d. k. Akäd. d. Wissensch. Math-naturw. Kl.*, Wien, 1904, cxiii, 537.

[3] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

The typical histological appearance of the pars anterior from a case of *dystrophia adiposogenitalis* is shown in figure 161. The cells are shrunken and widely separated, just as they are in the pituitary of the dog in which this syndrome has been produced by separation or compression of the infundibular stalk (fig. 111, p. 164).

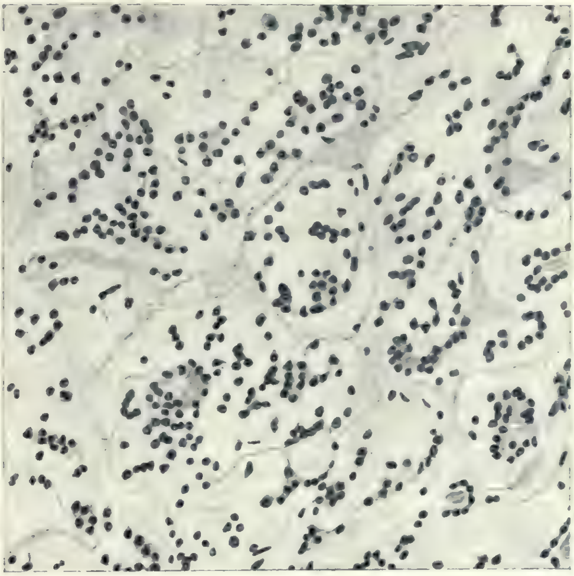


Fig. 161.

Section of the pars anterior from a case of *dystrophia adiposogenitalis* in a young man, showing intense atrophy of the cells. (*From a section kindly lent by E. E. Glynn.*)

× 150.

It appears, then, that the state of adiposity with genital atrophy is due to interference with secretory function or the blood-supply of the pituitary as a whole, and that some of the symptoms can be mitigated, as we have seen, by injections of infundibulin and some by the extract of the anterior lobe. Thus again we have evidence that the pituitary is one organ and not two.

PLURIGLANDULAR AFFECTIONS IN PRIMARY LESIONS OF THE PITUITARY

Of the physiological relationships between the pituitary and the other hormonopoietic organs we have had some proof in the extirpation experiments already recounted; and of the alterations which may occur in distant organs of internal secretion with pathological lesions of the pituitary we have had an indication in respect of the gonads, in which retrograde changes may form a characteristic symptom of the diseases in question. It will be well, however, shortly to consider the question in more detail, for undoubtedly some of the symptoms of hyperpituitarism and hypopituitarism are dependent not on the lesions in the pituitary but rather on those in other hormonopoietic organs.

Gonads.—We have seen that the metabolism of hyperpituitarism is largely concerned in the retention of the lime and magnesium salts. This is a masculine characteristic; consequently it is not surprising to find other evidence of emphasized male characterization in this state. Attention has been called to the fact[1, 2] that in the early stages of acromegaly in men there is often increased sexuality. No doubt this is directly dependent on the hypophysial lesion. In women, on the other hand, hyperhypophysism causes the immediate cessation of menstruation, and in a short time the assumption of male secondary characteristics.

There can be little doubt, then, that there is a close connexion between the gonads and the pituitary; and the difference in the two sexes is interesting, and may in part be related to the effect pituitary lesions are believed to have on the suprarenals.

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[2] Buday, K., and N. Iansci, *Deutsch. Arch. f. Klin. Med.*, 1898, lx, 385.

Tandler and Grosz[1], as we have seen, came to the conclusion that hyperhypophysism follows hypoplasia in the gonads—no doubt from the fact that ablation of the ovaries leads to eosinophilia and hyperplasia of the pars anterior. I have already discussed this question and have pointed out the unlikelihood of this suggestion representing the true state of the case.

Cushing[2] discusses the relative importance of the interstitial cells of the gonads and the reproductive cells, and appears to attach undue importance to the interstitial cells in the production of the secondary sex-characteristics. I have adduced evidence elsewhere[3] which proves conclusively that these cells have very little influence, if any, in this respect. However, in regard to the subject under discussion, the matter is only of importance in connexion with the integrity of the uterus which is dependent on the interstitial cells, and bears no relation to sex-characterization, which may be directly influenced by the pituitary as well as by other members of the hormonopoietic system.

In the later phases of acromegaly, when there may be hypopituitarism, there is in both sexes genital hypoplasia and a tendency towards a neutral type in regard to the secondary sex-characteristics.

Suprarenals.—It is well known that the suprarenal cortex has an important influence on sex-characterization[3, 4, 5], and the medulla a pressor action on the blood-pressure.

In many cases of pituitary disease there seems to be associated asthenia, with a low blood-pressure and pigmentation. In these circumstances the suprarenals have been found to be very small. A typical case of this character is shown in figure 162. The patient was deeply pigmented—even having patches on the sclerotics—and the other symptoms of Addison's disease were pronounced; at the same time there was well-marked acromegaly. Cushing[2] records cases in which 'hypersuprarenalism' existed in association with hypopituitarism.

In a case, from which I have had the opportunity of

[1] Tandler, J., and S. Grosz, *Wien. Klin. Woch.*, 1907, xx, 1596.

[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[3] Bell, W. Blair, *The Sex Complex*, 1916.

[4] Bulloch, W., and J. H. Sequeira, *Trans. Path. Soc.*, 1905, lvi, 189.

[5] Glynn, E. E., *Quart. Journ. Med.*, 1912, v. 157.

examining sections, and in which a young woman developed masculine characteristics with amenorrhœa, there was a chromophobe adenoma in the pars anterior of the pituitary (fig. 163) and a hyperplastic tumour in the suprarenal cortex (fig. 164). Both these lesions would produce masculinity in a woman, and increased masculinity in a man. In the case recorded there were no symptoms other than those mentioned.

FIG. 162.

A case of combined Addison's disease and acromegaly in a man.

Thymus.—Experimental evidence has shown that destructive lesions of the pituitary are associated with a normal or hyperplastic thymus; but, on the other hand, we must remember that after oöphorectomy or removal of the testes there is eosinophil hyperplasia in the pars anterior together with enlargement of the thymus. This apparently paradoxical state of affairs indicates that probably the thymus is unaffected by affections of the pituitary, and that if it be enlarged in these circumstances this is due to the genital hypoplasia which coexists with most pituitary lesions.

Thyroid.—The results of experimental thyroidectomy and partial removal of the pituitary lead us to conclude that the

thyroid and pars anterior are closely related, and that as an immediate result of the extirpation of one of these organs there is a change in the other; this, however, is much more decided in the pituitary than in the thyroid.

It has already been mentioned (p. 232) that Furnivall has found the thyroid affected in a large number of primary pituitary lesions.

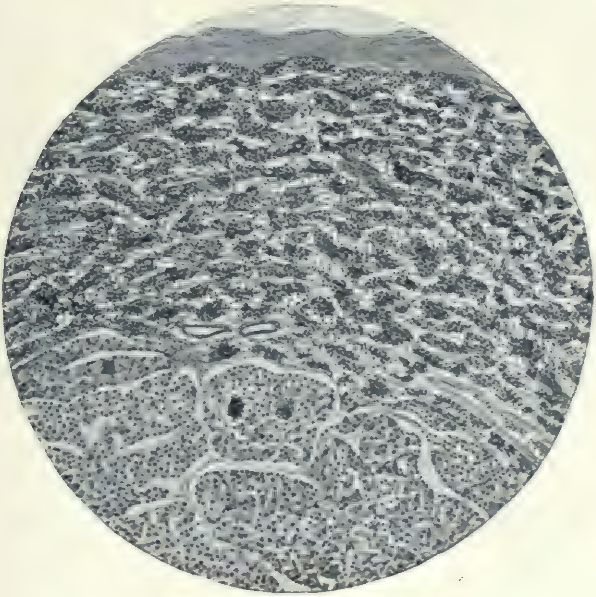


FIG. 163.

Section of the pars anterior of the pituitary of a young woman who had developed masculine characteristics, showing a chromophobe tumour in the lower part. (*From a section kindly lent by J. Anderson.*)

× 60.

Pineal.—We have no definite information of any connexion between pituitary lesions and affections of the pineal. It is, however, believed from experimental and pathological evidence that the pineal is related to the development of sex-characteristics, and that a decreased function in this organ before puberty leads to sexual precocity in boys. It is doubtful whether the pineal has any genital functions after puberty, or is related to the alterations in the sexual functions and characteristics associated with pituitary lesions.

FIG. 164.

Section of the suprarenal of a young woman who developed masculine characteristics, showing encapsuled hyperplasia in the lower part of the picture. (*From a section kindly lent by J. Anderson.*) × 60.

PRIMARY LESIONS IN THE PITUITARY PRODUCING SYMPTOMS NEITHER OF EXCESSIVE NOR OF DIMINISHED SECRETION

It not infrequently happens that extensive lesions occur in the pituitary body which are associated with but few symptoms. In these circumstances the patients may complain only of disturbances of vision, but sometimes they suffer also with headaches. As a rule, therefore, they consult an oculist in the first instance.

In one case of this character, which came under my notice, the patient, an unmarried lady 42 years of age, was completely blind in the left eye and had a very restricted field of vision in the right eye. At no time had there been either vomiting or headache. The menopause had occurred somewhat prematurely a few years previously. The patient had never exhibited symptoms either of acromegaly or of *dystrophia adiposogenitalis*. There was a moderately raised carbohydrate-tolerance (200 grammes of lævulose), but this is not unusual after the menopause. There was no thermic reaction. The systolic blood-pressure was raised and was equal to about 140 mm. of mercury. A radiograph showed that the sella turcica was considerably enlarged backwards (fig. 165).

It is probable that in this case portions, at least, of every part of the pituitary were functionating, and that there was some cystic lesion present in the anterior lobe. The patient, however, refused operation.

There is a large number of these cases now on record; and they appear to be readily recognized by oculists as a typical class of case about which not infrequently they are consulted[1].

This seems, therefore, the most suitable place in which to

[1] Discussion, *Proc. Roy. Soc. Med.* (*Neurol. and Ophthalmol. Sects.*), 1913, vi, i.

discuss the causation of the ocular symptoms with which patients suffering from pituitary lesions are so often afflicted.

The matter is by no means an easy one; at the same time it is one of considerable moment, since a correct interpretation of the ocular anomalies may enable us definitely to decide in which direction the tumour is extending, and from which side the disease must be attacked when the temporal route is employed.

So far as I know, this point has rarely been adequately considered in all its bearings, the general assumption being that the

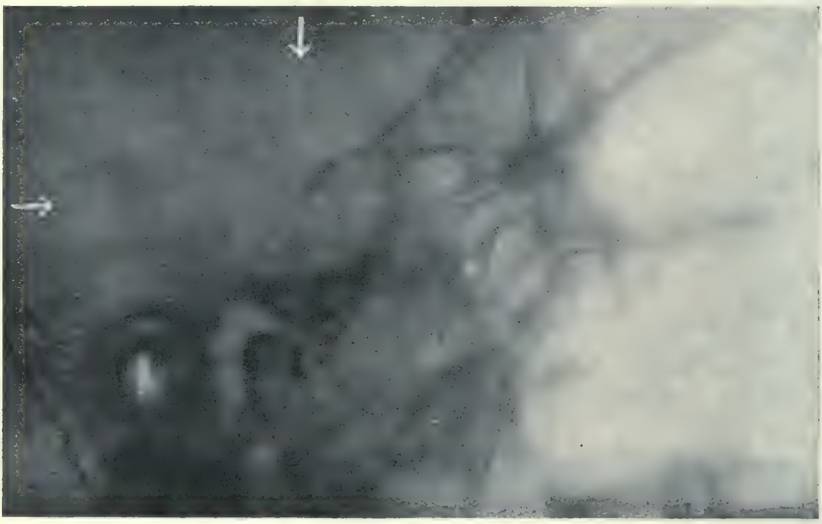


Fig. 165.

Radiograph of the skull of a woman complaining of loss of sight, showing considerable enlargement of the sella turcica. (*By Thurstan Holland.*)

$\times \frac{1}{1}$.

ocular symptoms, scotoma and hemianopia, are due to primary optic atrophy from the direct pressure on the chiasma produced by the enlarging pituitary. Such an explanation, however, is not entirely satisfactory, for a patient may become totally blind in one eye without the other being appreciably affected.

A short consideration of the anatomy of the optic tracts and of the oculomotor nerves is necessary to make clear the difficulties that may arise in connexion with this question.

It is generally accepted that the fibres connected with the

retinæ, on which sight depends, have a peculiar course; that is to say, those on the nasal sides of the retinæ decussate in the optic chiasma, as illustrated in figure 166, while those on the temporal sides have a more direct course, and are enclosed below and at the sides by the decussating fibres from the opposite eye. The nasal fibres of the maculopapillary bundle, which is concerned with acute vision at the macula, decussate, while those from the temporal side of the macula do not do so.

Now, the pressure of the enlarging pituitary body is exerted chiefly backwards, and only slightly forwards. This is shown in most radiographs by the erosion and destruction of the posterior clinoid processes and the posterior wall of the sella turcica (figs. 141, 143, 144, 160 and 165), due, no doubt, to the lesser resistance behind; consequently in these circumstances the pressure must be exerted *away from* the optic chiasma, and not entirely on it. But the enlargement and resulting pressure is not only backwards, but laterally as well.

If, however, the chiasma be involved the pressure of the growing tumour will affect the fibres from the nasal fields of the retinæ, and the anterior and posterior commissures of Stilling and Gudden respectively, which, however, are believed to be unconnected with vision. Pressure on the optic chiasma forwards will, then, usually produce the well-known ocular symptom of bitemporal hemianopia, since the rays of light from the temporal fields impinge, after passing through the lenses, on the nasal sides of the retinæ (fig. 166); and also in some cases central scotoma or scotomata may be caused by injury to the nasal fibres of the highly differentiated and easily damaged maculopapillary bundles, which pass through the chiasma. It is doubtful if the direct (temporal) fibres can be much affected by pressure in this region. On the other hand, as already indicated, it is certainly more usual for the optic tracts to be involved by extension backwards and laterally of the pituitary enlargement.

Fisher[1] has shown that the field of vision is not only first limited on the temporal side, but also from above downwards; further, this writer[2] agrees with Cushing[3] that the colour-vision

[1] Fisher, J. H., *Trans. Ophth. Soc. Unit. Kingdom*, 1911, xxxi, 51.

[2] Fisher, J. H., *Proc. Roy. Soc. Med.* (*Neurol. and Ophthalmol. Sects.*), 1913, vi, liii.

[3] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

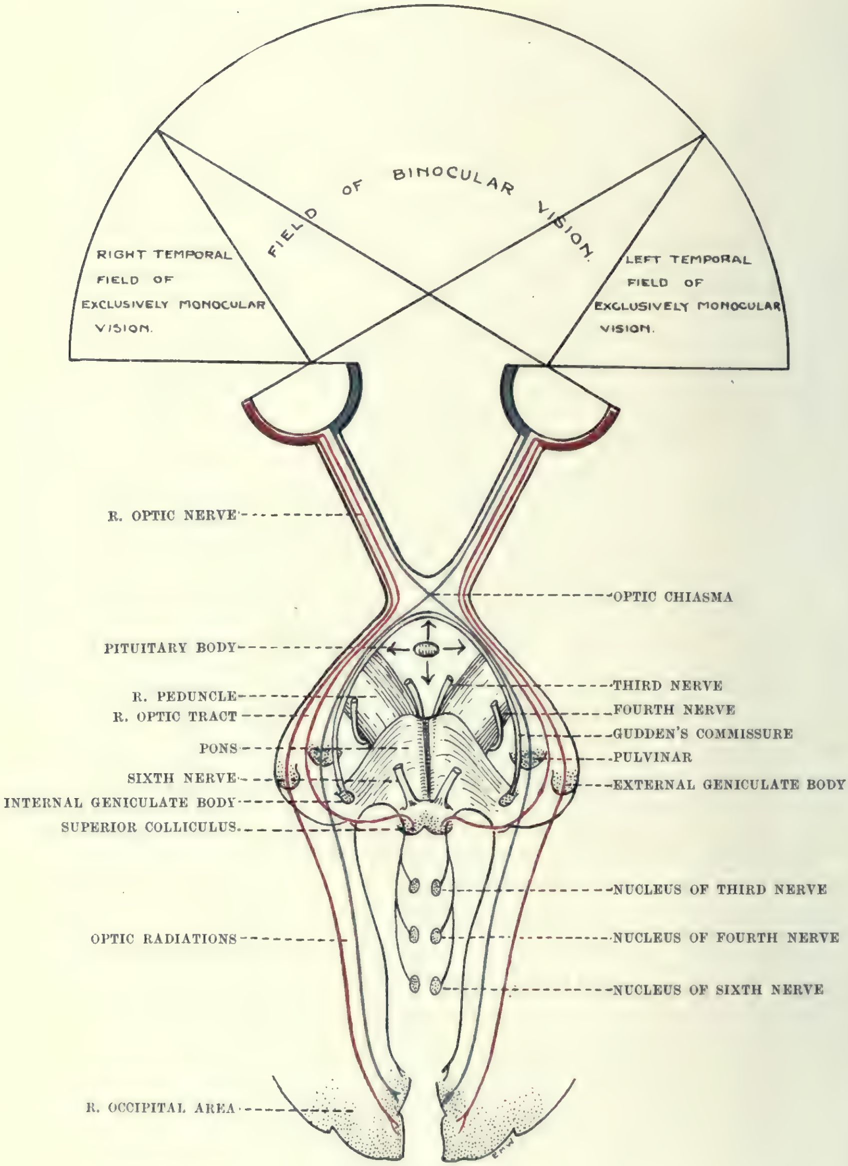


FIG. 166.

Diagram illustrating the optic nerves and tracts and the fields of vision. The possible directions of extension of enlargements of the pituitary are shown by arrows.

disappears before the form-vision. Fisher[1] states that in his opinion the ocular symptoms can be only explained on the assumption that there is a dragging or stretching of the fibres in the optic tract of the side opposite to that on which direct pressure is being exerted. He says: "My cogitations are leading me to the conclusion that the visual phenomena in many of the cases are explained by traction effects on the visual pathways as the tumour extends upwards behind the chiasma and between the optic tracts in the interpeduncular space. A tumour fairly symmetrical in outline would stretch the decussating fibres in the chiasma, while in no way dragging on the direct fibres, and give us a bitemporal hemianopia; it is conceivable that the highly specialized function of the macular fibres might be more readily injured than that of the other fibres in the chiasma; on a traction hypothesis the expanding scotoma cases are to be understood, and hemiachromatopia can be recognized as a symptom which it would be very difficult to accept on a direct pressure hypothesis. If the tumour mass, having already caused a bitemporal hemianopia, increased now more to the right than to the left side, it would probably drag on the left optic nerve as a whole, or accentuate the angle between the left optic nerve and the left optic tract; in either way the fibres from the temporal half of the left retina would now suffer by dragging, and the eye would be rendered blind; the tumour expanding to the right would diminish the acuteness of the angle or curve formed by the right optic nerve and the right tract, and the uncrossing fibres from the right retina might long preserve their function. A pituitary tumour growing in the interpeduncular space asymmetrically and from the first lying more to the right than to the left of the median line might, I think, be expected to injure by traction first the decussating fibres from the left optic nerve and then its non-decussating fibres before any fibres of the right optic nerve became unduly stretched; as the crossing fibres from the right retina became involved, loss of temporal field on this side would be expected to occur, either centrifugally or centripetally. The possibility that a displaced optic nerve may receive injurious pressure from the bony optic foramen on that side towards which it is displaced

[1] Fisher, J. H., *Proc. Roy. Soc. Med.* (*Neurol. and Ophthalmol. Sects.*), 1913, vi, liii.

can also be conceived. In the rarer cases of homonymous hemianopia direct pressure on the optic tract concerned is, no doubt, the true explanation; in the tract the uncrossed fibres seem to be afforded the more sheltered situation."

Further, I do not think it has been sufficiently emphasized how frequently there is some degree—often very considerable—of oculomotor paresis on one side. The close relationship of the third nerve to the pituitary (fig. 166) accounts for the great frequency with which it is involved in the pressure produced by an enlarging pituitary tumour. I think, too, that in the paresis of this nerve, which produces the symptoms of external squint with diplopia and possibly nystagmus, we have the most important evidence as to the direction in which the tumour is extending; that is to say, the lateral pressure is greatest on the side on which there is evidence of paresis of the third nerve.

Sometimes the fourth and sixth nerves are affected.

It is necessary, also, to bear in mind the possibility of indirect pressure from a large tumour, either of the pituitary or in the neighbourhood, on the lower visual centres (fig. 166). Such a phenomenon might lead to very confusing ocular symptoms.

§ ii. SECONDARY LESIONS OF THE PITUITARY

NEIGHBOURING PATHOLOGICAL CONDITIONS

Hydrocephalus.—Although Marienesco and Goldstein[1] in 1909, and later Goldstein[2] described cases of *dystrophia adiposo-genitalis* associated with hydrocephalus and supposed meningitis, to Cushing[3] belongs the credit of definitely calling attention to the connexion between hydrocephalus and pituitary lesions. The last-named surgeon quotes several illustrative cases. In one of these there was a cerebellar cyst giving rise to moderate ventricular hydrocephalus, and the symptoms pointed to hyperhypophysism—that is, acromegaly. In other cases of hydrocephalus from various causes—congenital and new growths—there was hypopituitarism.

We have seen (p. 245) that Cushing believes that hydrocephalus produces pressure on the posterior lobe, particularly through the infundibulum. But, as I have already stated, the infundibulum in man is not hollow; consequently the pressure should be evenly distributed on the pituitary as a whole, or on the blood-supply; and this is borne out by Cushing's own cases. In the first (case xxxviii) there was hyperhypophysism, due no doubt to irritation of the anterior lobe, for the ventricular pressure was only moderate. In the other cases the pressure was greater and the anterior lobe—according to the illustrations given—suffered equally with the posterior lobe; indeed, the whole appearance is that of a pituitary in which there had been interference with the blood-supply.

Neurath[4], also, has reported cases apparently of hyperplasia

[1] Marienesco, G., and K. Goldstein, *Nouv. Icon. de la Salpêtrière*, 1909, xxii, 628.
[2] Goldstein, K., *Arch. f. Psychiat.*, 1910, xlvii, 126.
[3] Cushing, H., *The Pituitary Body and its Disorders*, 1912.
[4] Neurath, R., *Wien. Klin. Woch.*, 1911, xxiv, 43.

in the anterior lobe with skeletal overgrowth in association with hydrocephalus.

Cushing raises another point which is open to criticism. He states that in these circumstances there is stasis in regard to the secretion of infundibulin; that the intraventricular tension is such that the secretion cannot be poured into the cerebrospinal fluid in normal quantities. As the whole question of the destination and method of conveyance of infundibulin to the body-fluids, and indeed, of the vital importance of this hormone is by no means settled, we are not in a position to discuss this matter further. Attention may be called, however, to what has been said from a physiological point of view on page 102 and following.

Fig. 167.

A cholesteatoma in the neighbourhood of the pituitary which exerted pressure on that organ and so caused *dystrophia adiposogenitalis.* (*From a specimen kindly lent by E. E. Glynn.*)

$+ \frac{1}{1}$.

Neighbouring tumours.—A growth such as a glioma or an endothelioma, or possibly a gumma, in the neighbourhood of

the pituitary may give rise to some of the symptoms of pituitary tumours, especially headaches and ocular disturbances. With these we are not at the moment concerned. But neighbouring tumours may produce pressure on the pituitary and lesions therein. If the pressure be moderate there may be glycosuria and other symptoms of hyperpituitarism; when the pressure is

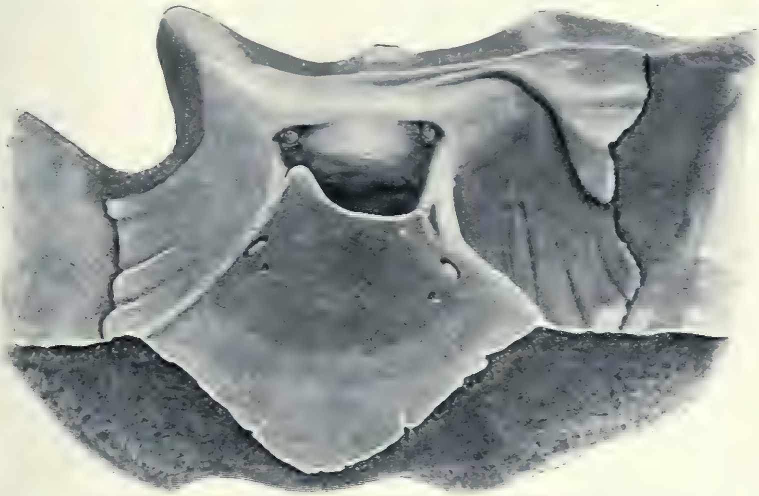


Fig. 168.

Erosion of the right posterior clinoid process caused by the tumour shown in figure 167. (*From a specimen kindly lent by E. E. Glynn.*)

$\times \frac{1}{1}$.

considerable hypopituitarism will be caused. If the growth be more or less centrally placed (fig. 167) diagnosis may be somewhat difficult, although a radiograph should show little or no enlargement of the sella turcica, and this would help us to exclude a primary pituitary lesion. Nevertheless, even in these circumstances the posterior clinoid processes may be eroded (fig. 168) —a lesion which may lead to the supposition that the pituitary fossa is enlarged in a backward direction, as is usually the case with a primary pituitary tumour.

DISEASES OF THE OTHER HORMONOPOIETIC ORGANS

Lesions of the thyroid.—From the close relationship between the pituitary and thyroid, to which attention has been directed, we would expect to find that the pituitary is affected in diseases of the thyroid, which are very common in women; and such is the case.

I have had the opportunity of examining the organs from a case of a *cretinism*, and as the appearances of the pituitary are somewhat remarkable it may be worth while to describe them in some detail.

In this case—a female subject, 33 years of age—the pituitary was found on macroscopical examination to be about the maximum average size in an adult, measuring 1·5 cm. in the antero-posterior diameter and 0·7 cm. in the superior-inferior diameter. Unfortunately the transverse diameter was not recorded, but it appeared to correspond with the other measurements.

On histological examination the first point noted was that the organ is enclosed in a dense fibrous tissue capsule, from which it cannot readily be separated. The pars anterior is for the most part composed of chromophobe cells; there are extremely few eosinophil cells, and only occasional collections of lightly staining basophil cells around the periphery. Large masses of secretion, which appear to be formed by a syncytial confluence of chromophobe cells, are scattered throughout the pars anterior (fig. 169). A considerable number of colloid-acini are to be seen in the pars intermedia, and there is much neutrophil granular secretion underlying the pars intermedia and extending in a branching fashion into the pars nervosa (fig. 170), the neuroglia-fibres of which have a 'teased-out' appearance.

These characteristics of the intrinsic structure of the pituitary indicate considerable activity, which is probably compensatory in character.

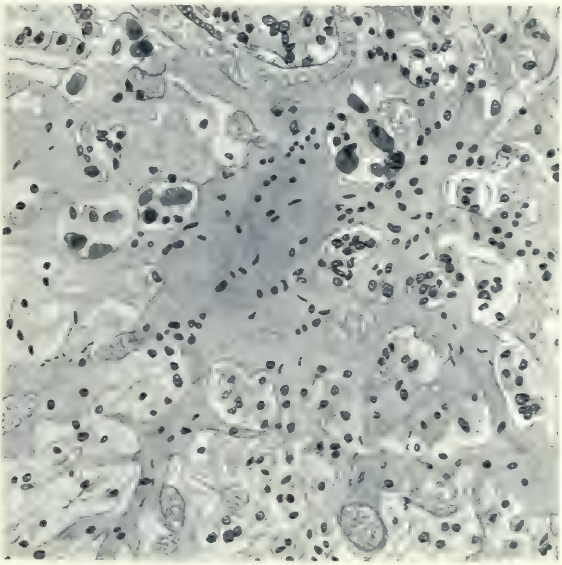


FIG. 169.

Section of the pars anterior of a cretin, showing masses of secretion among chromophobe cells and a few basophils.

× 200.

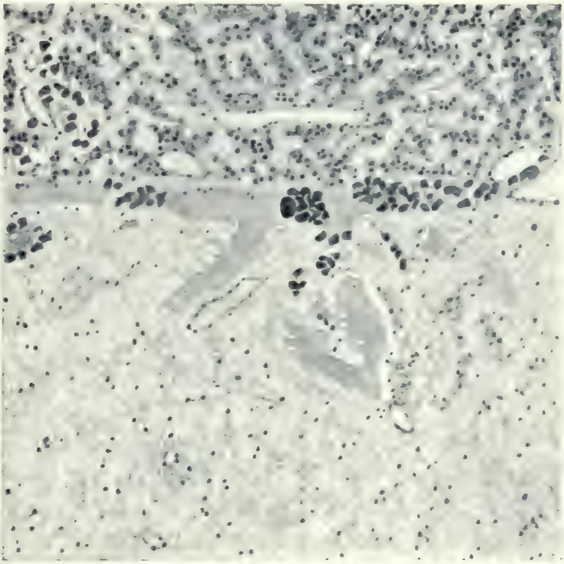


FIG. 170.

Section of the pituitary of a cretin, showing secretion extending from the pars intermedia into the pars nervosa.

× 100.

In *myxœdema* associated changes in the pituitary were first described by Boyce and Beadles[1] and by Comte[2]. They observed general enlargement of the organ and found histologically an increase in the chromophobe cells in the pars anterior, and they noted, also, the masses of secretion that I have already mentioned as occurring in the cretin. Fry[3], too, has recently described the pituitaries from two cases of myxœdema. He found changes somewhat similar to those which I have already specified. There was, however, in his cases eosinophil as well as basophil colloid in the pars anterior, and a large number of basophil cells.

It appears probable from the scanty evidence before us that there is a very considerable increase in the activity of the pituitary as shown by the histological appearances of the pars anterior in cretinism, and a rather less pronounced, but similar, change in myxœdema, in which disease there are different degrees of insufficiency, but never entire suppression of the thyroid function as in cretinism.

In *parenchymatous goitre*, in which condition there is presumably a low degree of thyroid activity, I have found in the pars anterior universal chromophobia with a well-marked acinous arrangement in the cells enclosing secretion (fig. **171**), and neutrophil colloid in the pars intermedia (fig. **172**). The pars nervosa appears to remain normal in these circumstances.

Fry[3] has described the pituitary from a patient with goitre, the histological appearances of which were those of a cystic adenoma. In this case there was a large number of eosinophil cells in the pars anterior, and in the pars posterior there was a considerable amount of colloid. These phenomena indicate a moderate degree of thyroid insufficiency with the required compensatory effort on the part of the pituitary.

In *exophthalmic goitre* I have found in the pars anterior many more basophils than normal ; indeed, most of the cells appear to be basophil (fig. **173**), with, perhaps, a few in a transitional stage between eosinophilia and basophilia. The pars posterior is normal. This appearance indicates, of course, a condition of inactivity ; and is in keeping with what has already been said

[1] Boyce, R., and C. F. Beadles, *Journ. Pathol. and Bacteriol.*, 1893, i, 223.

[2] Comte, L., *Zeigler's Beitr. z. Pathol. Anat.*, 1898, xxiii, 90.

[3] Fry, H. J. B., *Quart. Journ. Med.*, 1915, viii, 277

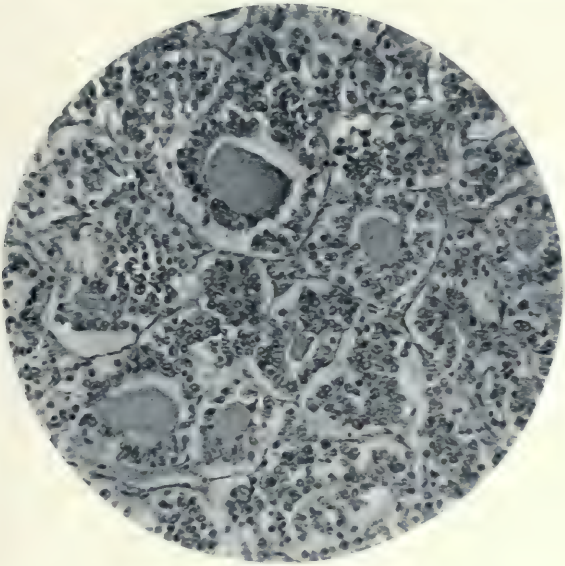


Fig. 171.

Section of the pars anterior in a case of parenchymatous goitre, showing an acinous arrangement of chromophobe cells. (*Photomicrograph.*)

× 150.

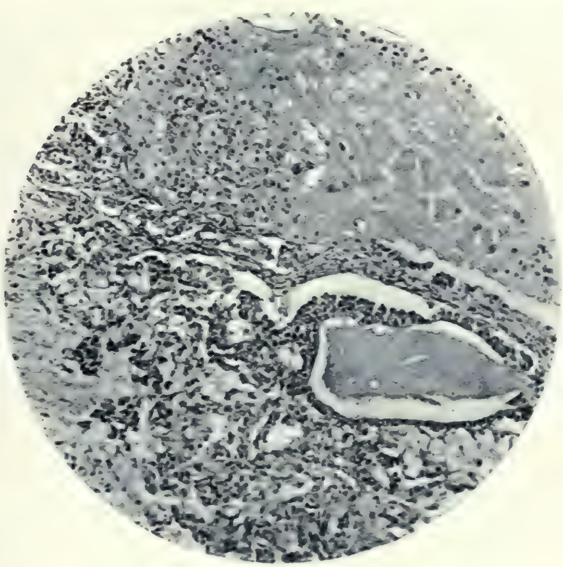


Fig. 172.

Section of the pituitary in a case of parenchymatous goitre, showing neutrophil colloid in the pars intermedia. (*Photomicrograph.*)

× 100.

in regard to the relationship between the thyroid and pars anterior of the pituitary.

Lesions of the gonads.—We have already seen that Tandler and Grosz[1] and others assert that acromegaly is the result of insufficiency in the secretory functions of the gonads, but I regard this view as untenable. It cannot, however, be denied that changes occur in the pars anterior as the result of ovarian and testicular insufficiency—we have ample experimental evidence

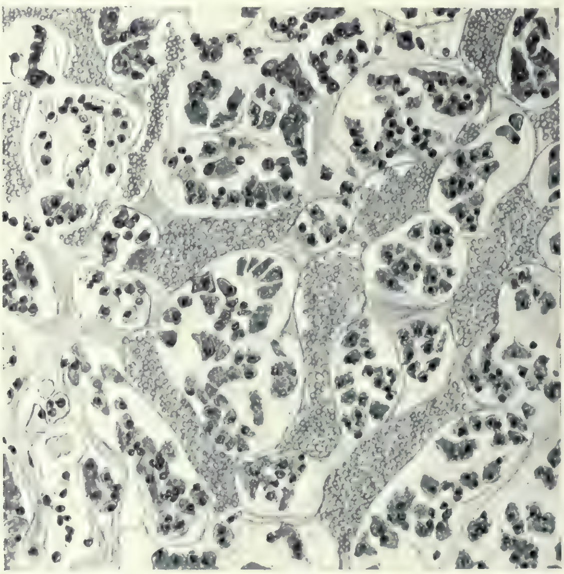


FIG. 173.

Section of the pars anterior in a case of exophthalmic goitre, showing collections only of basophil cells separated by large blood-sinuses, and shrunken owing to imperfect fixation.

× 200.

pointing in this direction; and the evidence indicates that with insufficiency in the gonads there is increased eosinophilia in the pars anterior.

It is possible that the skeletal overgrowth which may occur when puberty is delayed owing to retardation in the development of the gonads is occasioned by hyperplasia in the pituitary, but of this we have but little definite pathological evidence.

[1] Tandler, J., and S. Grosz, *Wien. Klin. Woch.*, 1907, xx, 1596; *idem*, 1908, xxi, 277.

It is probable, however, that the gonads and pituitary are antagonistic to some extent, although the integrity of either is dependent on the normal functional activity of the other. It is certain, also, that correlated changes only occur in the pituitary when the functions of the gonads are in excess of or below the normal: we have no direct evidence concerning the changes that may occur in the pituitary in the first case; but in the second there is an obvious increase in the secretion of the pars anterior, as is shown by the eosinophilia found in these circumstances.

Lesions of the thymus.—The only abnormal condition of the thymus of which we have any specific knowledge is that in which the thymus fails to undergo the normal involution that is believed to commence early in life and to reach the maximum about puberty. In some cases the thymus not only fails to undergo this involution, but even undergoes hypertrophy with hyperplasia, producing the well-known condition of *status lymphaticus*. This exists to some extent in eunuchs and in all castrated animals.

I do not think that many observations have been made in regard to possible changes in the pituitary in these circumstances. In one case that I have investigated there was also a parenchymatous goitre, to which the alterations found in the pituitary were probably due. In another case of *status lymphaticus* in a young woman who died suddenly the genital organs and functions were normal, and no changes were detected in the pituitary. Fry[1] records a case in which he, too, failed to observe any abnormality; and Cushing[2], also, records two cases in which there were pituitary tumours, but in which it was difficult to trace any relationship between these lesions and the hyperplasia in the thymus.

It appears likely on the evidence before us, especially of the associated genital hypoplasia which may be present, that if any changes were to be found in the pituitary as the result of the *status lymphaticus* they would be of the nature primarily of an increased function with appropriate changes in the cells of the pars anterior.

[1] Fry, H. J. B., *Quart. Journ. Med.*, 1915, viii, 277.

[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

Lesions of the suprarenals.—We have already seen that acromegaly may be associated with lesions of the suprarenals, but no satisfactory pathological evidence of changes in the pituitary as the direct result of Addison's disease or hyperplasia of the suprarenals has been adduced. In the case recorded by Anderson[1] there were hyperplastic lesions both in the suprarenal cortex and the pars anterior of the pituitary (p. 249).

Lesions of the pancreas.—Glycosuria is so often associated with disease of the pituitary that only in those cases in which definite lesions in the pancreas have also been found in diabetes can we look upon changes in the pituitary as possibly secondary to the pancreatic lesion.

Fry[2] has made a number of investigations in which the lesions in the pancreas were carefully investigated. He came to the conclusion that histological changes in the pituitary are unnoticeable with acute pancreatitis, but that with diabetes (presumably of pancreatic origin) there is in the pars anterior an increase in the eosinophils, which assume an adenomatous arrangement, and that there is " colloid invasion of the anterior lobe, and areas of cellular degeneration ". The cellular degeneration mentioned could hardly be specific, and may have been due to imperfect fixation of the tissues.

[1] Anderson, J., *Glas. Med. Journ.*, 1915, lxxxiii, 178.
[2] Fry, H. J. B., *Quart. Journ. Med.*, 1915, viii, 277.

METASTASES

Sometimes pituitary lesions are the result of metastatic growths from distant sites. As a rule, the symptoms produced are those of destructive or irritative lesions of the pituitary. As Fischer[1] emphasizes, there is great individuality in regard to various malignant tumours: sometimes metastases produce secretion, at other times they do not; some malignant tumours of the pituitary cause acromegaly, and others do not.

It is, however, hardly likely that a metastatic growth could produce an excess of secretion of the pars anterior, as a primary growth may do; for secondary growths invariably have the structural characteristics of the parent growth, and if they possess any secretory activity it is of the same quality as that produced by the original neoplasm.

An interesting example of the irritative effect that may be caused by a metastatic growth in the pituitary, is that recorded by Simmonds[2]. The patient, a woman, from whom a breast had been removed two months previously for cancer, developed obstinate and intense polyuria. The quantity of urine passed varied from 10 to 19 litres a day. At the necropsy the pars nervosa was found to be entirely destroyed by a cancerous metastasis. This author states that the growth irritated the pars intermedia, and so caused diabetes insipidus (polyuria) with which the patient suffered.

Metastases interfering with the blood-supply of the pituitary may cause *dystrophia adiposogenitalis*, should the patient survive a sufficiently long period of time.

[1] Fischer, B., *Hypophysis, Acromegalie und Fettsucht*, Wiesbaden, 1910.

[2] Simmonds M., *Munch. Med. Woch.*, 1913, lx, 127.

INFECTIONS

We have seen in our experimental studies that general and even local infections may affect the pituitary enough to produce definite changes akin to hyperplasia in the pars anterior; and we find that these observations are borne out by pathological investigations in the human subject.

Many observers [1, 2, 3] have considered that infection is an etiological factor in the onset of some cases of acromegaly—that is to say, hyperhypophysism is often secondary to infectious diseases. Typhoid, especially, is believed to be capable of producing a lasting effect owing to the long duration of the disease.

It is possible, therefore, that functional hyperplasia takes place as a means whereby secretion in large quantities may be produced for the neutralization of toxins; and, according to some, this hyperplasia may fail to disappear with the termination of the infection.

In general septicæmia I have found very obvious changes in the pars anterior of the pituitary: the cells are swollen and cloudy, and for the most part have a neutrophil reaction to stains. These chromophobe cells are often arranged in a very definitely acinous manner, such as we see normally in pregnancy. The basophil cells may exist in fair numbers at the periphery, but there are very few eosinophil cells.

In more localized infections, such as that producing a cerebral abscess, exactly the same state of affairs may be observed; but in the cases examined the chromophobe cells were not found to be arranged in glandular formation as is the case in severe generalized infections.

Cushing[3] states that animals from which parts of the pars

[1] Messedalgia, L., 1908 (quoted by Cushing[3]).

[2] Delille, A., *L'hypophyse et la medication hypophysaire*, Paris, 1909.

[3] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

anterior had been removed succumbed more easily to infections than normal animals. This, however, must have been a difficult matter to prove satisfactorily.

There is one phenomenon, which is supposed to result from the hyperplasia of the pars anterior due to infections, that is of peculiar interest. I refer to the growth that takes place in young persons in whom the epiphyses have not joined at the time they become affected by some prolonged infectious disorder, such as typhoid fever. This remarkable growth, which may be represented by an increase in stature of several inches in a few weeks, has been attributed to the hormone which originates in the pars anterior and stimulates the growth of bone. The pituitary, excited to excessive action by the toxin, produces the hormone in larger quantities than normal, and thus, it is supposed, brings about the result described.

It is only right to say that this view has been seriously questioned, and has no experimental support; Chanal[1], indeed, asserts that the increase in growth which may occur, particularly in typhoid fever, is due to the infective processes directly stimulating the epiphyses.

It is important to note that infections not only lead to hyperplasia, but may in some cases be so intense as to cause atrophy or necrosis of the pituitary. Such a condition has been described by Simmonds[2]. The patient died at the age of 46 years. Ten years previously she had suffered with severe puerperal fever, following her fifth confinement. Subsequently, there was complete amenorrhœa, and mental symptoms developed, with loss of weight and general weakness. At the post-mortem examination the pituitary was found to weigh only 0·3 gramme, and on histological examination very few normal cells were to be seen in the pars anterior.

Simmonds states that he has frequently found in the pituitary bacterial emboli and necrosis in these cases.

[1] Chanal, J., 1907 (quoted by Cushing, *The Pituitary Body and its Disorders* 1912).

[2] Simmonds, M., *Deutsch. Med. Woch.*, 1914, xl, 322.

TOXÆMIAS OF PREGNANCY

The toxæmias of pregnancy are little understood in regard to the etiological factors; consequently in recording coincidental changes in the hormonopoietic organs we have no clear knowledge as to the cause of the lesions. Nevertheless, alterations in the pituitary associated with toxæmias of pregnancy are undoubtedly secondary to the general toxæmia whatever that may be.

I know of no observation or description of the pituitary in *hyperemesis*—that is, excessive vomiting of pregnancy.

In *eclampsia* I have had opportunities of making observations, and I have found that in this condition there is an abnormal number of basophils in the pars anterior, and a considerable eosinophilia (fig. **174**), whereas the so-called 'pregnancy' neutrophil cells are not well marked. We would expect, at the late stage of pregnancy at which eclampsia occurs, to find normally a considerable number of large neutrophil cells and very few basophils. The eosinophilia, of course, is often considerable in pregnancy, and is not abnormal.

Colloid is found in the pars intermedia and in the cleft (fig. **175**), as is usual. There may be, too, extensive invasion of the pars nervosa by the cells of the pars intermedia (figs. **175** and **176**).

The paucity of large neutrophil cells in eclampsia indicates, then, a lower degree of activity than is normal; while the invasion of the pars nervosa may lead to an excessive production of infundibulin.

In a case of *cortical necrosis of the kidneys*—a very rare complication of pregnancy, and one which is certainly due to some toxæmia—I found the general quantitative relationship between the neutrophil, basophil and eosinophil cells to be that normal to the pregnant state; but there was a considerable degree

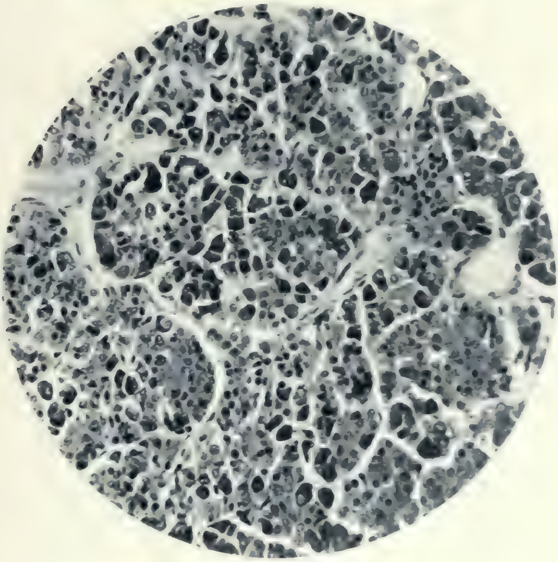


FIG. 174.

Section of the pars anterior in a case of eclampsia, showing a predominance of basophil cells. (*Photomicrograph.*)

× 100.

FIG. 175.

Section of the pituitary in a case of eclampsia, showing colloid in the pars intermedia and cleft, and invasion of the pars nervosa by the cells of the pars intermedia. (*Photomicrograph.*)

× 30.

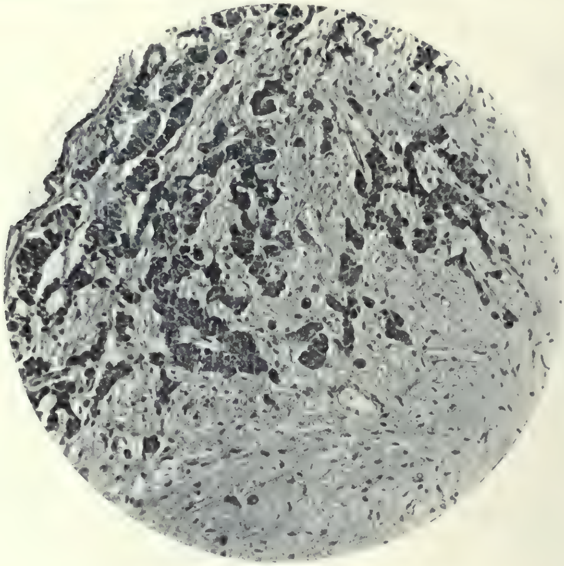


FIG. 176.

Section of the pars posterior in a case of eclampsia, showing masses of pars intermedia cells invading the pars nervosa. (*Photomicrograph.*)

× 60.

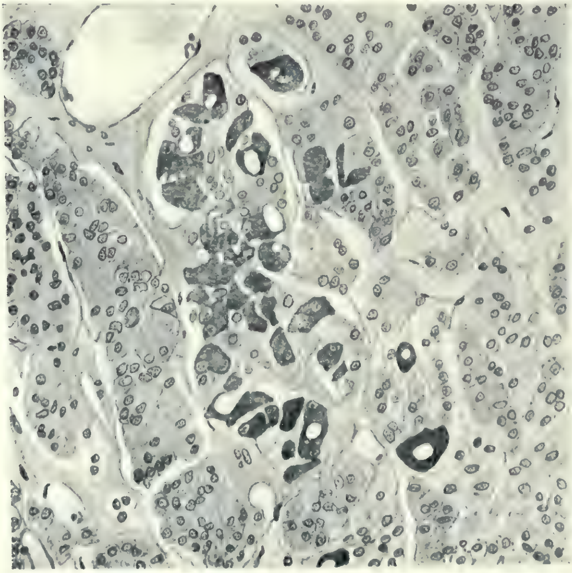


FIG. 177.

Section of the pars anterior in a case of cortical necrosis of the kidneys, showing vacuolation of the basophils.

× 200.

of vacuolation of the cells, which was most obvious in the basophils, owing to the colour-contrast (fig. 177).

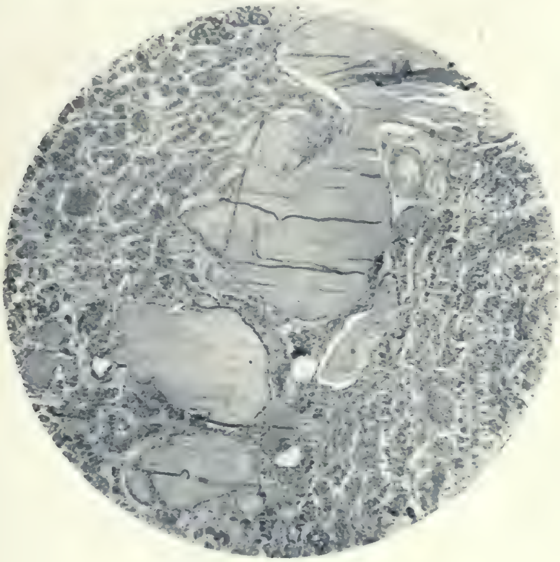


FIG. 178.

Section of the pars intermedia in a case of cortical necrosis of the kidneys, showing a large amount of colloid.

× 40.

There seemed to be a rather excessive quantity of colloid in the pars intermedia (fig. 178), although this substance is generally plentiful in this situation during pregnancy.

§ iii. GENERAL CONSIDERATION OF THE PATHOLOGY OF THE PITUITARY

In all that has gone before it has been very evident that our knowledge of pathological lesions of the pituitary is still imperfect and uncertain. And it is unlikely that we shall reach a more scientific standpoint until pathologists realize that no post-mortem examination is complete until all the hormonopoietic organs have been exhaustively examined. We know, also, still too little of the age-changes and sex-differences in the normal pituitary. Further, we have not yet conclusively and unanimously decided exactly what the situation and nature of the lesion is in many cases which we associate with hyperpituitarism and hypopituitarism ; and we are still confused by the supposed morphological and physiological separation of the different parts of the pituitary. Personally, I believe it to be one organ, and that it has many functions, just as all the other hormonopoietic organs have ; indeed, I believe that until we recognize the physiological unity of the pituitary body, we cannot reconcile what we now look upon as the conflicting facts of morphology, physiology and pathology in regard to this structure.

If the anterior and posterior lobes were separate and distinct organs, we would expect to find more evidence of their independent importance in comparative anatomy. We sometimes find, however, the reverse state of affairs—striking examples being, from one point of view, the absence of a pars nervosa in some elasmobranchs, and, from the other, the channelling of the pars nervosa by the cells of the pars intermedia in the monotreme (*ornithorhynchus*) (figs. **35** and **36**, p. **57**).

So, too, with respect to the physiology of the pituitary, the whole sum of the evidence obtainable—which I need not reiterate—points in the same direction.

Then, when we come to difficult pathological questions we find

the obsession concerning the duality of the different lobes of the pituitary still overshadowing us.

Thus Cushing states that hydrocephalus may produce hypopituitarism from secretory stasis in the pars nervosa. But before this explanation can be accepted we must understand how it is that other tumours in the neighbourhood of the base of the brain not acting in the same way may produce a similar train of symptoms. Further, we have seen that neither removal of the anterior lobe nor of the posterior can produce this state : interference with the whole blood-supply in the stalk is necessary. Again, it has been pointed out—for the most part by Cushing[1] himself—that the lowered body-temperature in *dystrophia adiposogenitalis* can only be raised by an extract of the *anterior* lobe ; while the low blood-pressure can only be raised, and the carbohydrate-tolerance reduced, by an extract of the *posterior* lobe.

This observer, therefore, in one sentence sweeps aside his own conclusions and the conclusions of others based on the assignment of syndromes to one or other part of the pituitary, instead of to the whole organ.

To press the point a little further : It is common knowledge that in the development of the pituitary body the epithelial structures are all derived from the ectoderm ; consequently the anterior lobe and the pars intermedia have the same origin. From our histological observations we know that the pars intermedia is closely related physiologically to the pars anterior—so much so that the cells of both secrete a similar substance. Further, it is often difficult to say where the pars intermedia begins and the pars anterior ends, for at the point of junction the cells appear to change almost imperceptibly from one type to the other. It has always been my opinion that the active principle of the posterior lobe is secreted by the cells of the pars intermedia. We have evidence, too, in an experiment of Vincent[2], that an extract of the central portion of the pars nervosa is much more active in its pressor effects than is the extract made from the periphery and the cells of the pars intermedia, which is comparatively inert. We have had evidence, also, that the secretion of the pars intermedia passes into the pars nervosa. Whether the secretion passes on entirely into the third ventricle, as

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[2] Vincent, Swale, *The Internal Secretions*, 1912.

described by Herring[1] and Cushing[2], which, however, I regard as doubtful, or whether the larger portion passes into the blood-vessels of the pars nervosa which are seen in such profusion in the ox (fig. 40, p. 62), as seems most likely, is of little importance in regard to the question we have in hand. But it is of considerable importance that the secretion of the pars intermedia does pass into the posterior lobe ; and that the pars intermedia does secrete a substance similar to that secreted by the anterior lobe.

It seems highly probable, therefore, from the evidence at our disposal, that the secretion of the pars intermedia is changed into a pressor substance as it passes through the posterior lobe ; and that the colloidal substance found among the cells of the pars intermedia and the secretion found in the cleft is ot the same character as that secreted by the anterior lobe. If this be so, we arrive at the principle I have so often enunciated—a principle which is of the greatest importance in the interpretation of diseases of the pituitary body—I mean that the pituitary body is one organ. Much that is supposed to be obscure becomes clear : for instance, insufficiency of the hormone from the pars nervosa can in many cases be accounted for by insufficiency of the cells of the pars anterior and the pars intermedia, which I believe to be fundamentally the same physiologically as they are anatomically. In these circumstances there would be an insufficient supply of secretion to the pars nervosa, in the substance of which the secretion of the pars intermedia undergoes alteration and acquires pressor qualities. No pressure, therefore, on the pars nervosa need be presumed to account for posterior lobe insufficiency—a state of affairs which can be relieved by the injection of infundibulin. So, too, from the other point of view, it is easy to understand the reason why in acromegaly, in which disease there is admittedly hyperplasia in the anterior lobe, we so frequently see polyuria and glycosuria. In accordance with the view just expressed an excess of secretion may pass into the pars nervosa and thence, after being converted into infundibulin, into the blood.

The acromegaly-syndrome may be summarized from this point of view. Some of the symptoms—the gigantism and bony

[1] Herring, P. T., *Quart. Journ. Exper. Physiol.*, 1908, i, 121.
[2] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

changes with the acral enlargements, the coarse skin, the genital stimulation are all due to the direct influence of the hyperplasia in the partes anterior and intermedia. The polyuria and the glycosuria are caused by the increase in the amount of secretion of the pars intermedia, which is passed into the pars nervosa and subsequently absorbed.

With regard to the other condition—*dystrophia adiposo-genitalis*—which is seen with destructive lesions that impair the blood-supply and produce hypopituitarism, the entire secretion is greatly reduced. The failure of secretion refers not only to that which is passed directly into the blood, but also that which is passed into the pars nervosa. We have seen, indeed, that at least one of the symptoms—the subnormal temperature—is relieved by the extract of the anterior lobe, and others—namely, the excessive carbohydrate-tolerance, and the low blood-pressure—by infundibulin.

This explanation of the interrelationships between the various portions of the pituitary body is, therefore, no idle hypothesis. It is based on morphological grounds, on all the best of the histological work that has been done, and on all the clinical data that are at our disposal. Practically, it makes clear many of the apparently contradictory features of hyperpituitarism and hypopituitarism. It explains, too, why with cystic changes in the anterior lobe, even with great enlargement and sella deformation, the pressure symptoms may only be those of any tumour in the interpeduncular space—so long as normal cells exist in sufficient quantity to produce the necessary secretion. In these cases, too, the pars nervosa is usually crushed, yet—provided there are normal cells of the pars anterior, as I have just said—no intrinsic symptoms of pituitary origin are evident.

This point of view—founded on, and compatible with, all the evidence at our disposal—should, if correct, in the future do much to render intelligible the pathology of the pituitary body.

§ iv. TREATMENT OF PITUITARY LESIONS

The treatment of pituitary disease is partly medical and partly surgical.

It may be stated that medicinal methods are only indicated to relieve certain metabolic and distant phenomena, and that they are of little value when there are local symptoms, such as headache and visual disturbances—these require relief by surgical procedures.

MEDICAL TREATMENT OF PHENOMENA DUE TO PITUITARY LESIONS

Hypopituitarism.—Medicinal treatment at the present time largely resolves itself into the supplementation of the deficient secretion. No doubt in a majority of cases the best results are obtained with whole-gland extracts. Supplementary medication will be discussed more fully in connexion with the therapeutical uses of pituitary extracts.

It is extremely difficult permanently to reduce the sugar-tolerance by medicinal means, but the psychical and sexual disabilities are often removed: mental torpor disappears; menstruation and potency return.

As the preparation must be administered over a considerable length of time oral administration is generally practised. Very large doses may be necessary: Cushing[1] states that he has administered 100 grains of whole-gland extract three times a day.

Glandular administrations are frequently of value after operations for the relief of local pressure-symptoms in lesions producing hypopituitarism.

I have observed an objectionable effect that is often produced

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

by glandular extracts—especially extracts of the pars anterior—namely, intense headache. This, however, has been most noticeable in those minor cases of hypopituitarism, in which amenorrhœa was the only obvious symptom.

Cushing found in one case after the failure of oral administrations that daily hypodermic injections of whole-gland extract, in a dose representing 2 grains of the dried extract, produced an amazing effect in regard to the mental and physical vigour of the patient.

In the same patient a graft from the pituitary of a child dying in child-birth was subsequently implanted in the subcortical tissues of the temporal lobe with permanent benefit, in spite of the discontinuance of hypodermic medication.

Hyperpituitarism.—The medicinal treatment of this condition is not satisfactory, except in the presence of a pluriglandular syndrome which beckons unmistakably to the extracts of the organs whose secretion is diminished.

Thyroid extract has, however, often been given with advantage, especially in cases of arrested acromegaly.

Kelladey[1] records a case of acromegaly in a woman, in whom intravenous injections of ovarian extract induced the return of menstruation with subsequent conception.

[1] Kelladey, L., *Zentralbl. f. Gynak.*, 1913, xxxvii, 1030.

SURGICAL TREATMENT OF PITUITARY LESIONS

SURGICAL ANATOMY

We have seen that the modern experimental procedures designed for the removal of the whole or of part of the pituitary are not difficult to carry out by the intracranial (bitemporal) route in the case of dogs owing to the fact that in this animal, which is also of a fair size, the organ rests in a very shallow fossa ; but that in an animal, such as the cat, in which the pituitary fossa is deep, the intracranial method is impracticable. Further, we have seen that the buccal route is invariably unsatisfactory because the operator cannot control by sight his manipulations in regard to the pituitary, and in any case he cannot do more than blindly destroy the whole structure or remove a portion of the pars anterior, and because there is, also, an almost inevitable risk of sepsis from the buccal cavity, with fatal meningitis. Thus it has come about that no experimental results obtained by operative procedures have been found worthy of acceptance, except when they have been practised on one species of animal (dog), and by the route of election (bitemporal) in that animal.

It will readily be realized, then, that in man, in whom the pituitary is situated in a deep fossa, which is closely guarded on every side by nerves, arteries and large venous channels, suitable access has been found difficult to obtain. As a result, many different directions have been chosen by surgeons for attacking pituitary lesions in the human subject (fig. 179). These various routes will be discussed presently, but before we consider them in detail it will be worth while to study a few details of the surgical anatomy of the parts.

First, when the *temporal route* is chosen it should be remembered that the temporal lobe is situated in a deep concave

fossa, and that the brain must be raised before the edge of the sella turcica can be reached; and further, that when the sella is reached the pituitary disease cannot be attacked owing to the depth of the fossa unless the lesion extend upwards.

Second, with regard to the *frontal intracranial route,* it will be evident that when the frontal lobes are to be raised the success of the operation will depend greatly on the production of a low intracranial pressure, and that by this route it is

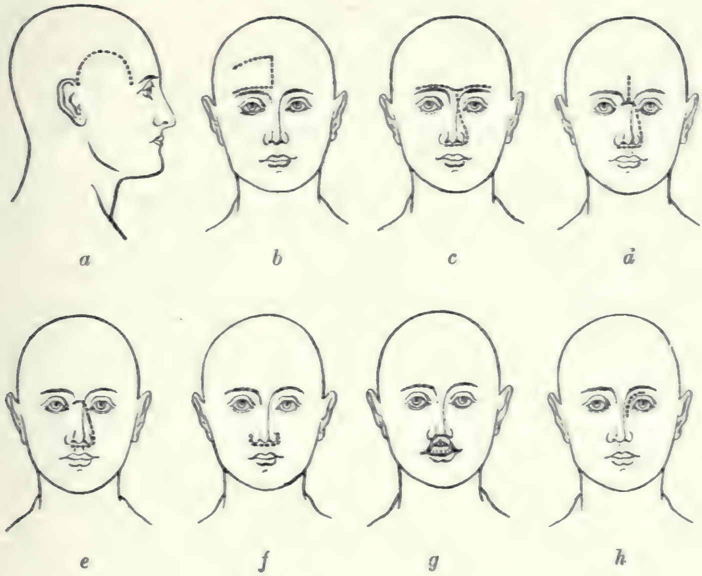


FIG. 179.

Incisions (shown by dotted lines) for the various procedures that have been adopted. *a*, Horsley-Paul temporal method; *b*, Frazier orbitofrontal method; *c*, Eiselsberg first superior nasal method; *d*, Eiselsberg second superior nasal method; *e*, Schloffer-Eiselsberg superior nasal method; *f*, Kanavel inferior nasal method; *g*, Halstead-Cushing sublabial method; *h*, Chiari-Kahler orbitonasal method.

impossible satisfactorily to deal with a pituitary lesion that does not extend upwards.

Third, with respect to the *nasal routes,* we shall see that some are much better than others owing to the differences in regard to the possibility of minimizing the risk of sepsis and the degree of mutilation inflicted. But the operative procedures by this route are not always easy because of the variations that may occur in the anatomy of the parts.

With this difficulty in mind, Gibson[1] has made a careful investigation of the principal measurements in relation to the pituitary fossa in 107 skulls, apparently without distinction as to sex. He also paid particular attention to the character of the sphenoidal sinuses and to the floor of the sella turcica. Cope[2], too, has recently studied these questions, also without regard to sex.

Although no doubt surgeons with large experience in operations on the pituitary by the nasal route—of whom there are at present only a few—are able to accommodate themselves to the varying circumstances, Gibson's and Cope's figures and observations are of considerable value to the less experienced operator. At the same time, the fact has not been adequately emphasized by these writers that pituitary lesions by pressure and extension downwards may alter considerably the character of the floor of the sella turcica, and the relation of it to the sphenoidal cells.

Gibson gives the following average measurements (fractions omitted), which, with very few exceptions in regard to the larger measurements, were found not to vary to the extent of one centimetre :—

Nasion to sella turcica[3]	62 mm.
Nasion to posterior surface of sella turcica	75 mm.
Anterior nasal spine to sella turcica[4]	78 mm.
Anterior nasal spine to clivus	88 mm.
Length of the pituitary fossa	12 mm.
Depth of the pituitary fossa	6 mm.
Depth of the sphenoidal sinus on the line from the anterior nasal spine to the sella turcica	18 mm.

These and other measurements are shown in figure 180; but fractions have been omitted.

With regard to the variations in the sphenoidal sinuses, which are illustrated in figure 14 (p. 23), Gibson gives the following particulars.

Complete or practical absence of sinuses (fig. 14, *b*) occurs in

[1] Gibson, W. S., *Surg. Gynæcol. Obstet.*, 1912, xv, 199.

[2] Cope, V. Z., *Brit. Journ. Surg.*, 1916, iv, 107.

[3] Cope (*loc. cit.*) found the average of this measurement to be 60·1 mm.

[4] Cope (*loc. cit.*) found the average of this measurement to be 76·19 mm.

3 per cent.; small sphenoidal sinuses in 9 per cent.; no projection of sinuses *beneath* the sella turcica (fig. 14, *d*) in 22 per cent. of all cases examined. The fact that in these variations the floor of the sella does not bulge into the sphenoidal sinuses might cause difficulty in the determination of its position. He also found that in 2 per cent. of the cases there was a *transverse* sphenoidal septum (fig. 14, *e*), which might be mistaken for the roof of the sinuses.

When the sphenoidal sinuses project beneath the sella turcica, and have thin posterior walls (fig. 14, *c*), these may be pierced by the operator, and the pons injured.

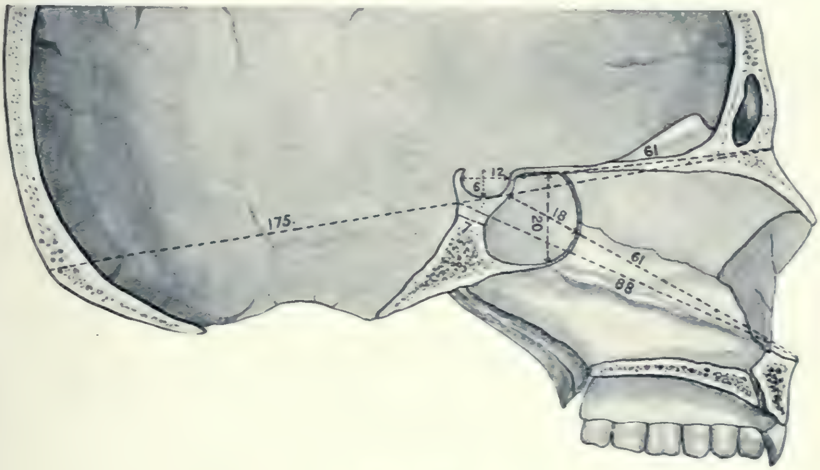


Fig. 180.

Sectional measurements of the skull in relation to the sella turcica and sphenoidal sinuses. The figures are accurate, but the skull is reduced approximately by one-half.

Besides these vagaries the cribriform plate may dip down unduly, and, by obscuring the direct line of attack, cause the operator to divert his course below the sella turcica; or a deflected septum may cause him to miss the correct median approach.

INDICATIONS FOR OPERATION

The following symptoms demanding interference must be shown to be dependent on enlargement of the pituitary, or on lesions situated in the neighbourhood of, and affecting, the pituitary.

(*a*) Symptoms due to increased general intracranial pressure, such as headache.

(*b*) Symptoms due to local pressure, such as blindness, oculomotor palsy and ' pituitary headache '.

(*c*) Symptoms due to disturbances of the pituitary secretion producing acromegaly or *dystrophia adiposogenitalis.*

SELECTION OF THE ROUTE OF APPROACH

The method adopted for approaching the pituitary should depend, to a great extent, on the special reason for operation. Thus, general intracranial pressure must be relieved by an intracranial method, whereas the relief of ' pituitary headache ' and the evacuation of pituitary cysts are better effected by the nasal route ; consequently an accurate diagnosis of the condition present is the first step in the selection of a route by which the lesion may be reached and the symptoms relieved. The direction of extension of the lesion may, too, be a matter of importance. To a certain extent, also, the surgeon should be influenced in his choice of direction by the anatomical conformation of the sphenoid and sphenoidal sinuses. A good radiograph conveys the necessary information in regard to this matter.

In spite of these associations which should guide the surgeon in the selection of a method of approach, it appears that most operators have a route of election for every case. Schloffer[1], Proust[2], Cushing[3], and more recently Cope[4], have discussed the subject, but it is evident that no final decision has yet been reached as to the indications for the different routes.

[1] Schloffer, H., *Beitr. z. Klin. Chir.*, 1906, l, 767.

[2] Proust, R., *Journ. de Chir.*, 1908, i, 665.

[3] Cushing, H., *The Pituitary Body and its Disorders*, 1912 ; Weir Mitchell Lecture : *Journ. Amer. Med. Assoc.*, 1914, lxiii, 1515.

[4] Cope, V. Z., *Brit. Journ. Surg.*, 1916, iv, 107.

PREPARATION OF THE PATIENT

In all operations on the pituitary hexamethylenamine (foramine) should be administered for some days before and after operation to render the cerebrospinal fluid antiseptic (see p. 129).

Lumbar puncture as a preliminary operative procedure is extremely useful for reducing the intracranial pressure if more than decompression is to be attempted. Moreover, the over-

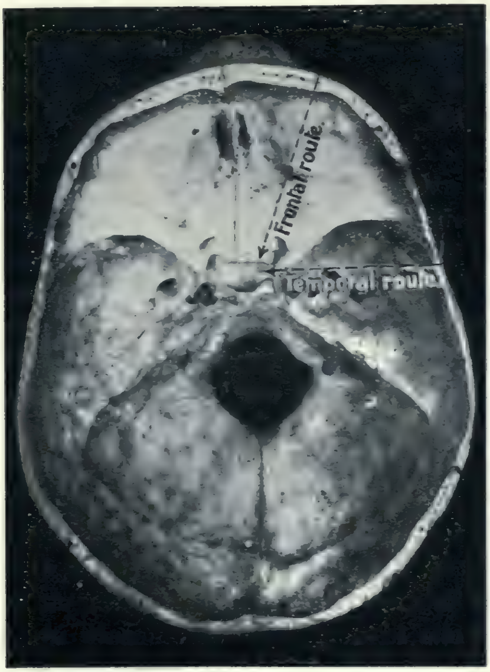


Fig. 181.

Base of the skull, showing the directions followed in the intracranial methods of approach to the sella turcica. (*Photograph.*)

hanging-brain position (fig. 184, p. 295) suggested by Karplus and Kreidl[1], may be used to facilitate the surgical manipulations.

The other general preparations need no special description.

INTRACRANIAL METHODS

Two directions have been chosen for reaching the pituitary intracranially in the human subject—the temporal and the fronto-orbital (fig. 181).

[1] Karplus, J. P., and A. Kreidl, *Wien. Klin. Woch.*, 1910, xxiii, 309.

Temporal and bitemporal routes

The actual procedures in regard to this operation on the human subject need not be recapitulated, for they correspond almost exactly with those which have been adopted in experimental operations on animals, and have already been fully described and illustrated (p. 129 and following).

This method of approach, as emphasized by Cushing[1], is unquestionably the best for the relief of general intracranial pressure ; indeed, this surgeon advises that a temporal decompression operation should always be performed when the intracranial pressure is great, even though it be thought advisable subsequently to attack the actual lesion by another route, for in those cases in which headache is very severe, and is associated with a choked optic disc, superimposed on optic atrophy, a pituitary tumour is generally present and is extending upwards. It must be remembered that the so-called 'pituitary headache' differs from the headache associated with general intracranial pressure in that it is caused by local pressure in the pituitary fossa.

As a method of approach for operations on the pituitary in the human subject the temporal (fig. 179, *a*) has not secured much favour. It was originally suggested by Horsley[2] as the result of his experimental experiences, and Paul[3] was the first to employ the procedure in the human subject. Paul's operation—the first undertaken for pituitary disease—was attempted for the relief of severe headache in a case of acromegaly under the care of Caton in the Liverpool Royal Infirmary on February 2nd, 1893. The operation was not carried further than simple decompression, by the removal of a portion of the temporal bone. The headaches were relieved, and the patient lived for three months subsequently. Henceforth, the possibilities of surgical procedures came to be fully recognized, and Horsley himself performed operations on the human subject by the same route. The details of his results were never published, but so far as is known they were not satisfactory.

Cushing[1], too, has performed a few operations on the

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[2] Horsley, V., *Lancet*, 1886, i, 5.

[3] Paul, F. T., and R. Caton, *Brit. Med. Journ.*, 1893, ii, 1421.

pituitary by the temporal route—apart from simple decompression measures—and he has come to the conclusion that this method should not be the one of election for dealing with pituitary growths in general. He states that in the entire series of his cases, as published in his book, " in only one patient . . . did post-mortem study indicate that a lateral subtemporal operation would have offered the only chance of surgical relief "[1]. This case was one in which there was an infundibular cyst situated above an otherwise normal pituitary. The only symptom was bitemporal hemianopia. The patient died from meningitis on the thirteenth day after an attempted transphenoidal operation.

Orbitofrontal route

This method of approach, originally put forward by Krause[2] and McArthur[3], and perfected by Frazier[4], has lately received considerable support, and was utilized by Cope[5] in the three operations performed by him. Erdmann[6] and Elsberg[7], also, have employed this method with slight modifications. The technique of Frazier's operation is as follows.

The patient is anæsthetized with ether—first by the open, and afterwards, when anæsthesia is complete, by the intratracheal method. He is then placed with the shoulders on a pillow over the top of which the head is allowed to fall back (overhanging-brain position), and the frontal sinuses are transilluminated to show their size. Next, an incision is made extending along the supraorbital ridge from the external angular process to the nasion ; from this point the incision is carried vertically upwards beyond the hair-line almost to the summit of the frontoparietal suture, and then outwards at right angles over the frontal bone till a point is reached vertically above the external angular process where the skin-incision was commenced (figs. 179, *b* and 182). The skin, subcutaneous and pericranial tissues are now

[1] Cushing, H., *The Pituitary Body and its Disorders*, 1912.

[2] Krause, F., *Deutsch. Klin.*, 1905, viii, 1004.

[3] McArthur, L. L., *Journ. Amer. Med. Assoc.*, 1912, lviii, 2009.

[4] Frazier, C. H., *Ann. Surg.*, 1913, lvii, 145 ; *Surg. Gynæcol. and Obstet.*, 1913, xvii, 724.

[5] Cope, V. Z., *Brit. Journ. Surg.*, 1916, iv, 107.

[6] Erdmann, J. F., *Ann. Surg.*, 1914, lix, 452.

[7] Elsberg, C. A., *Ann. Surg.*, 1914, lix, 454.

retracted far enough to permit the formation of an osteoplastic flap which is turned outwards after the bone has been cut through by means of a trephine and wire-saw. The periosteum of the roof of the orbit is separated, and the supraorbital ridge is divided by means of converging incisions, in order that a wedge-shaped piece of bone may be removed (fig. 182), which will fall into position on replacement without the need of fixation. With

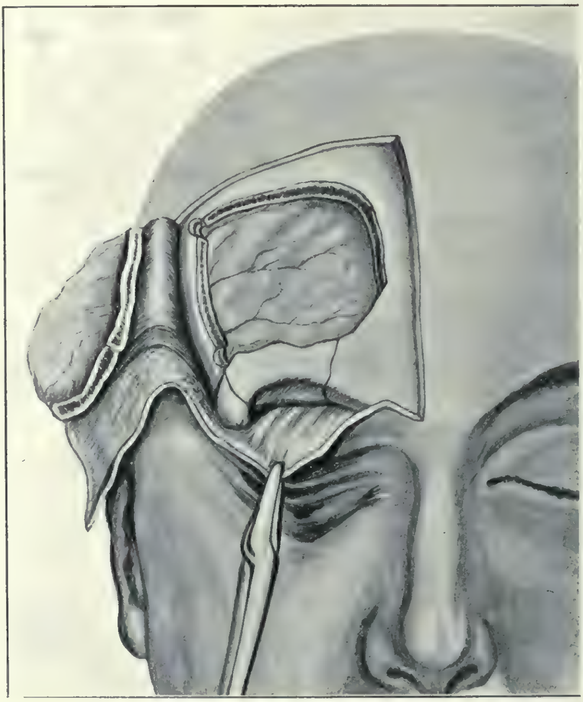


Fig. 182.

Frazier's orbitofrontal method of approach to the pituitary. (*After Frazier.*)

this piece of the ridge the anterior portion of the roof of the orbit is resected. The posterior part of the orbital roof as far back as the optic foramen is now removed with a rongeur.

This exposure permits the operator to displace the orbital contents downwards and outwards, and to raise the frontal lobe without opening the dura mater. If, however, the intracranial tension be great and a preliminary lumbar puncture have not been performed, a small opening may be made in the dura to

allow the cerebrospinal fluid to escape. The frontal lobe is then raised with a retractor—preferably spoon-shaped (fig. 87, p. 135) —until the optic nerve is seen leaving the cranial cavity; at this point the dura is incised and the retractor slipped through the opening thus made in order that the pituitary region may be fully exposed.

At the conclusion of the operation the supraorbital fragment is replaced and the osteoplastic flap sutured in position.

It is claimed that by this route suprasellar lesions can easily be attacked, and the general intracranial pressure relieved. The orbitofrontal competes, therefore, with the temporal method.

EXTRACRANIAL METHODS

Nasal (transphenoidal) routes

Schloffer[1] first suggested reaching the pituitary by way of a nasal route. The interest aroused by this method of procedure is shown by the enthusiasm with which it has been adopted and modified (fig. 183). The techniq ıe of these operations may be described under two headings.

Superior nasal methods.—This route, which was originally advocated by Schloffer[1], if we except the experimental nasofrontal operation of Giordano[2], has been employed chiefly by von Eiselsberg[3]. The operation was at first performed by this operator in the following manner.

The posterior nares were packed to prevent the inhalation of blood. One incision through the skin was made across the brows bilaterally, and another, which joined the first incision at the root of the nose on the left side, was carried down the side of the nose and along the nasolabial furrow beneath the left nostril to the mid-line (fig. 179, *c*).

The nasal bones were cut through with a chisel. The septum —cartilaginous and bony—was then divided in such a way as to leave a large portion of the cartilage, ethmoidal plate and vomer to be turned over with the nose to the right side. This

[1] Schloffer, H., *Beitr. z. Klin. Chir.*, 1906, l, 767.

[2] Giordano, D., *Comp. di Chir. Operat. Ital.*, 1897, ii, 100.

[3] Eiselsberg, F. von, *Trans. Amer. Surg. Assoc.*, 1910, xxviii, 55; *Ann. Surg.*, 1910, lii, 1; *Arch. f. Klin. Chir.*, 1912, c, 8.

precaution retained subsequently a good 'bridge' for the nose. Next, the anterior wall of the frontal sinuses was raised through the transverse incision. The turbinate bones and ethmoidal cells were excised, and the operator then came down upon the anterior wall of the sphenoidal sinus. This and the anterior wall of the floor of the sella turcica were removed and the pituitary exposed. Later, Eiselsberg[1] performed much the same operation after making a slightly different incision (fig. 179, *d*) and, later still, by turning back the nose alone without interfering with

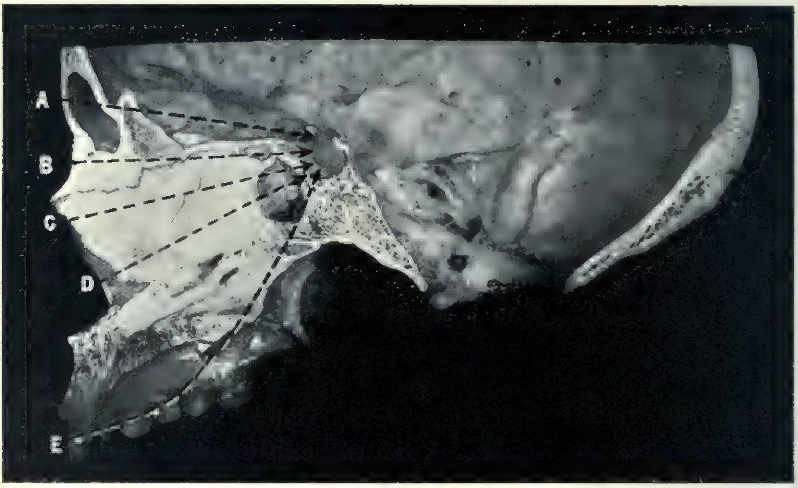


FIG. 183.

Vertical section through the skull, showing the direction of the chief routes by which the pituitary has been attacked from the front. A, Orbitofrontal route; B and C, superior nasal routes; D, inferior nasal route; E, buccal route.

the frontal sinuses. This last procedure has, however, been attributed to Schloffer (fig. 179, *e*).

These methods are unnecessarily mutilating and have been discarded in favour of the submucous inferior nasal procedures.

Inferior nasal methods.—Kanavel[2] was the first to show that it is possible to reach the pituitary fossa through the inferior nasal route. By this method the nose was turned upwards by means of a U-shaped incision which divided the nasolabial

[1] Eiselsberg, F. von, *Arch. f. Klin. Chir.*, 1912, c, 8.

[2] Kanavel, A. B., *Journ. Amer. Med. Assoc.*, 1909, liii, 1704.

junction (fig. 179, *f*). The cartilaginous septum was divided along the inferior border, and was partly raised and partly cut away from its attachment to the ethmoidal plate. Next, the middle turbinates were removed and the septum was deflected to one side. The anterior walls of the sphenoidal sinuses were then excised and the floor of the sella turcica was cut through.

Mixter and Quackenboss[1], who employed this route subsequently in the case of a pituitary tumour in a child, made the important modification of submucous resection of the septum—a procedure that lessened considerably the risk of sepsis.

Hirsch[2], basing his procedures on Hajek's[3] radical operation on the sphenoidal sinuses, modified the method by performing the operation through one nostril. The procedures were completed in several sittings. In the earlier steps the nasal septum, the middle turbinates and the ethmoidal cells, were excised, and the sphenoidal sinuses laid open; subsequently, the anterior wall of the floor of the sella turcica was removed, and the pituitary attacked. These procedures were all carried out under local anæsthesia. Later Hirsch[4] recommended the same operation with submucous resection of the septum.

Halstead[5], also, modified the original method of Kanavel by gaining access to the nasal cavity by means of a sublabial incision (fig. 179, *g*). The upper lip and nose were raised and the operation was performed through the aperture into the nares so created.

These modifications led to the perfected technique—now practised by Cushing[6] and others—which appears to be the best of all the nasal methods, combining as it does the principal advantages of several of the intranasal route procedures. Since this method is likely to be used extensively, the following particulars of the technique are worth recording.

After undergoing preliminary treatment for a few days with formamine the patient is anæsthetized with ether by the 'open'

[1] Mixter, S. J., and A. Quackenboss, *Ann. Surg.*, 1910, lii, 15; *Trans. Amer. Surg. Soc.*, 1910, xxviii, 94.

[2] Hirsch, O., *Wien. Med. Woch.*, 1909, lix, 636.

[3] Hajek, M., *Arch. f. Laryngol. und Rhinol.*, 1904, xvi, 105.

[4] Hirsch, O., *Journ. Amer. Med. Assoc.*, 1910, lv, 772.

[5] Halstead, A. E., *Trans. Amer. Surg. Assoc.*, 1910, xxviii, 73.

[6] Cushing, H., Weir Mitchell Lecture: *Journ. Amer. Med. Assoc.*, 1914, lxiii, 1515.

method. As soon as anæsthesia is complete this mode of administration is changed for the intratracheal method.

The patient is placed in the overhanging-brain position. The operator stands leaning over the top of the head.

First, the upper lip is pulled towards the surgeon and an incision an inch in length is made through the frænum, as suggested by Halstead. The lip and nose are retracted as the incision is carried down to the anterior nasal spine of the superior maxilla (fig. 184). Blunt dissection is employed to raise the soft tissues from the bony floors of the nasal cavities, and from the lower lateral aspects of the septum, great care being taken lest the mucosa be button-holed. Retractors with blades 6 cm. in length and 1·8 cm. in width are now inserted on either side to keep back the mucous membrane set free from the septum and inner aspects of the floors of the nasal cavities (fig. 185). Next, a strip of cartilage, the lower edge of the plate of the ethmoid, and a large portion of the vomer are cut away. A special dilator is then pushed into the cavity thus made while the lateral retractors are still maintained in position. By this means the turbinates are temporarily flattened and room is obtained for the subsequent steps of the operation. The lateral retractors are now removed and a suitable bivalve nasal speculum is inserted (fig. 186). With this in place, and by the use of a head-lamp, the sphenoidal attachment of the septum can be identified, and the sphenoidal sinuses opened by means of a nasal ronguer (fig. 186).

So far the principal danger has been lest the orientation should not have been properly determined, and the ethmoidal cells have been opened instead of the sphenoidal. This can be avoided by recognition of the posterior margin of the vomer, and by careful examination of the radiograph taken before operation, which should show the size and the relationships of the ethmoidal and sphenoidal sinuses. During the whole course of the operation it is absolutely imperative that the field be kept free of blood.

When the anterior and lower walls of the sphenoidal sinuses and their mucous linings have been removed, the roof is easily identified. Usually it is thin, and it may so bulge forwards from the pressure in the sella turcica above as practically to occlude the sphenoidal sinuses. The thin lamina of bone

Fig. 184.

Partly sectional view of the first stage of the submucous inferior nasal method of approach to the pituitary (P). (*After Cushing.*)

forming the roof of the sinuses and floor of the sella turcica is cut through, and the dura mater lining the fossa is incised with a hooked knife similar to that employed in experimental operations (fig. 88, p. 136). In this last stage some care is necessary lest a

FIG. 185.

Second stage of the submucous inferior nasal method of approach to the pituitary. (*After Cushing.*)

transverse sphenoidal septum be mistaken for the floor of the sella turcica. A good radiograph of the region should, however, reveal such an anomaly.

The pituitary is now exposed, and the operator can deal with

it as may be considered necessary. In some cases, in which relief from 'pituitary headache' is the object of the operation, nothing further is done—a sella decompression has been accomplished. In other cases a cyst may be evacuated or a portion of a hyperplastic gland removed for the relief of symptoms occurring in acromegaly.

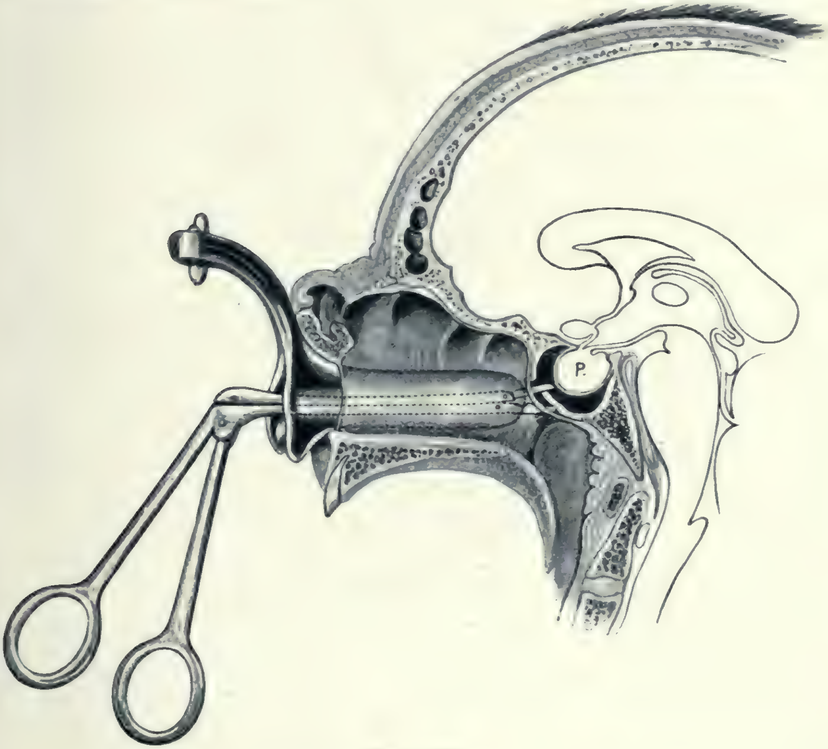


FIG. 186.

Third and fourth stages of the submucous inferior nasal method of approach to the pituitary. (*After Cushing.*)

At the conclusion of these procedures, after the operator has ascertained that there is no oozing of blood, the speculum is withdrawn and the parts are allowed to fall together. Two or three stitches are then used to close the initial sublabial incision. It is advisable lightly to pack the nares for a few hours in order to keep the septal mucosa in position and to prevent the accumulation of blood in potential spaces.

With regard to these operations by the nasal route it may be

said that only those procedures which are performed by the submucous methods can be conducted with any pretence of asepsis. Practically all the cases that are lost die from meningitis. Cushing's latest mortality figures are, however, so excellent that there can be little doubt that in suitable cases this is the safest and most convenient operation.

Orbital and orbitonasal routes

In 1910 I attempted experimentally to reach the pituitary through the orbit[1], after excision or displacement of the eye, and removal of the posterosuperior bony wall of the orbit. Owing to the limited space in small animals it was not found to be a suitable experimental procedure.

Kahler[2] has employed in the human subject a paranasal operation in which a curvilinear incision is made around the inner aspect of the orbit (fig. 179, *h*), and the eye retracted outwards. To some extent there is encroachment upon the nasal cavity, and this renders sepsis likely, although there is less danger than in the operation of a similar nature practised by Chiari[3] who removes the inner wall of the orbit and clears away the neighbouring ethmoidal cells.

Buccopharangeal route

Early investigators employed the buccal method of approach in their animal experiments ; but, partly owing to the frequent occurrence of sepsis and partly because of the limited view, these investigations have been held to be of little value.

It is, therefore, somewhat surprising to find that this method has been advocated for reaching the human pituitary in operative procedures. König[4] has described an operation of this nature. The soft palate is split, and a portion of the hard palate removed (fig. 183 E). In this way the base of the sphenoid is reached and the sella turcica opened.

The almost inevitable sepsis that must follow such a procedure renders its general adoption extremely unlikely, especially

[1] Bell, W. Blair, Hunterian Dissertation, *Roy. Coll. Surg., Eng.*, 1912.

[2] Kahler (quoted by von Szily, *Klin. Monats. f. Augenheil*, 1914, lii, 202).

[3] Chiari, O., *Wien. Klin. Woch.*, 1912, xxv, 5.

[4] König, F., *Berl. Klin. Woch.*, 1900, xxxvii, 1040.

in view of the fact that there are much safer and more suitable methods of approach.

RESULTS OF OPERATIONS

Cope[1] has collected the results of the principal operators with a view to determining which procedure has the least mortality. Naturally, there is an element of uncertainty that obtains in any such series, both in regard to the seriousness of the cases attacked and to the skill and experience of the operator. One fact stands out clearly, however, and that is that up to the present time the benefit derived from operation has rarely been permanent. Nevertheless, there is ample evidence to encourage surgeons to operate more frequently for pituitary disease.

From the following table, adapted from Cope's paper, it will be obvious that the palatal operation should never be attempted, while the orbitonasal procedure in a limited number of cases was free from mortality. But, on the other hand, we have insufficient information to tell us by which measure the greatest ultimate good can be accomplished so far as relief of symptoms is concerned.

TABLE XII

Method.	Operators.	Number of operations.		Deaths.		Mortality per cent.
Superior nasal	von Eiselsberg	16		4		25
Inferior nasal	Hirsch	26	132	4	12	9
„ „ Submucous	Cushing	106		8		
Temporal	Horsley	10	18	2	2	11
	Cushing	8		0		
Orbitofrontal	Frazier	4	26	0	2	7·7
	Cushing	16		1		
	Sargent	3		1		
	Cope	3		0		
Orbitonasal	Kahler	7	9	0	0	0
	Chiari	2		0		
Palatal	Preysing	6		4		66

It is obvious that in the future the benefits that will accrue from surgical interference will be directly proportional to the correct application of the most suitable method to the particular

[1] Cope, V Z., *Brit. Journ. Surg.*, 1916, iv, 107.

condition present, as determined by all the scientific methods of investigation at our disposal. At present, sufficient attention does not appear always to be directed to this all-important question of the nature, situation and exact direction and extent of the lesion which gives rise to the symptom or symptoms for which relief is sought. Enough has been said in connexion with the various operations to indicate the type of case for which the better methods are suitable.

PART IV

THE THERAPEUTICAL USES
OF
PITUITARY EXTRACTS

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THE THERAPEUTICAL USES OF PITUITARY EXTRACTS

§ i. GENERAL CONSIDERATIONS

THE extracts made from the pituitary have as many names as there are trade-firms manufacturing these products. I shall endeavour as far as possible to avoid the use of such terms for obvious reasons.

These extracts have been prepared from the whole gland, from the pars anterior alone, and from the pars posterior; consequently they may be described as extract of the whole gland, of the pars anterior, and of the pars posterior. If the most suitable and convenient nomenclature for these extracts could be generally adopted they would probably be described as pituitarin, hypophysin, and infundibulin respectively; but as already stated these and other terms have been so incorrectly and indiscriminately used by competing firms as to make this impossible[1]. The term 'infundibulin', however, which was

[1] In their propaganda for placing these products before the medical profession some firms have issued pamphlets which purport to give a *résumé* of the original work on which the various claims put forward in respect of the extracts are based. These accounts are often intentionally inaccurate, in that the literature quoted *refers only to work done with the preparations made by the firms concerned.* In this way credit has been wrongly given to, and assumed by, continental clinicians for what was discovered and described in this country at least a year before the first continental paper appeared; and, unfortunately, some medical writers appear to obtain their historical information from these pamphlets, rather than from the scientific literature on the subject. That section of the medical profession, too, which relies on trade-announcements for guidance in therapeutical matters should be warned against accepting the extravagant and often dangerous claims that have been made. It is only fair to add that there are, on the other hand, firms that publish accurate and reliable information.

originally introduced[1] for the extract of the pars posterior, will be used here.

METHODS OF MANUFACTURE

I am indebted for the following particulars concerning the preparation of pituitary extracts for the market to Dr. H. E. Annett of the Runcorn Research Laboratories.

Carefully selected, healthy glands are taken, and, after all the extraneous tissues have been removed, they are treated for the preparation of liquid extracts or of dried, powdered products.

Dried-gland preparations are obtained in the following way, according to the product required. The pars anterior or the pars posterior—which are easily separated—or the whole pituitary gland is finely minced in a sterilized mincing apparatus, and, after the ' wet weight ' has been noted, is dried *in vacuo* at a low temperature, and afterwards ground to a fine powder. The ' dry weight ' is then obtained, and the relation of this to the ' wet weight ' is recorded.

Liquid extracts.—The whole gland, or a portion of the gland, such as the pars posterior from which infundibulin is prepared, is extracted with saline solution. The albuminous matter is removed; the liquid is sterilized by filtration through unglazed porcelain, and then is distributed by bacteriological methods. The final preparation is again tested in regard to its absolute freedom from microorganisms.

The usual strength of the liquid extract in the case of infundibulin is 0·2 gramme in 1 c.c. of solution. In the case of liquid extracts of the pars anterior the strength is generally 0·5 gramme in 1 c.c. of solution.

Infundibulin and the extract of the pars anterior are not destroyed by boiling; consequently absolute sterility can always be ensured. In the case of infundibulin physiological tests are invariably carried out in regard to the effect on the blood-pressure and uterine muscle of each batch that is prepared. Should these tests be satisfactory the preparation is ready to be placed on the market.

[1] Bell, W. Blair, *Brit. Med. Journ.*, 1909, ii, 1609.

METHODS OF ADMINISTRATION

However valuable a drug may be when administered by the method of election, it may be comparatively, or completely, inert when introduced into the body in another way; consequently it is always of importance to know the method of administration that will give the maximum effect for the purpose required.

These differences are dependent to some extent on the chemical composition—often unknown—of the substance employed. Thus, suprarenal medullary extract is destroyed by the gastric juices, but the active principle of the thyroid gland is absorbed—so far as we know, unaltered—from the alimentary tract. On the other hand, both these extracts can be successfully injected into the subcutaneous tissues.

The method of administration, however, will depend—other conditions being equal—on the result required; if an immediate and maximum effect be desired the substance must be introduced directly into the blood-stream, or other tissues of the body, that it may be rapidly absorbed. Heaney[1] states that in his observations on the normal human subject, subcutaneous injections of infundibulin produced only a very slight rise in the blood-pressure and very little slowing of the pulse-rate. With intramuscular injections a definite rise in blood-pressure and some slowing of the pulse was observed. With intravenous injections great alterations were observed: in one case the blood-pressure rose within one and one-half minutes from 142 mm. to 200 mm. Hg, and the pulse-rate fell from 76 beats in a minute to 54.

I have observed[2] that relatively greater effects follow intramuscular injections in atonic conditions of the unstriped muscle-fibres than in normal circumstances.

If the substance be not destroyed by the digestive juices and a slow metabolic result be required, then oral administration is indicated.

In the case of the pituitary extracts administration is effected intravenously or intramuscularly[3] when a rapid result is necessary,

[1] Heaney, N. S., *Surg. Gynæcol. and Obstet.*, 1913, xvii, 103.

[2] Bell, W. Blair, *Brit. Med. Journ.*, 1909, ii, 1609.

[3] If injected hypodermically superficial sloughs may result from the intense local vasoconstriction; consequently infundibulin must be injected intramuscularly.

and orally when slow metabolic influences are required. It has already been stated that infundibulin is not destroyed by pepsin, but many believe that little, if any, of this substance is absorbed from the bowel. I have, however, seen very pronounced elevation of the blood-pressure follow prolonged oral administration. As with thyroid extracts, we would expect the active principles of the pars anterior to be absorbable from the alimentary tract since this structure is morphologically derived therefrom; but we have but little certain knowledge on this point, apart from the somewhat indefinite results which may follow.

Extracts of the pituitary are made, as we have seen, in the form of dried and liquid preparations. The dried extracts are usually given by the mouth, and the liquid intravenously or intramuscularly. There is, however, no reason against the oral administration of the liquid extracts; indeed, in the form of an elixir pituitary extracts are often prescribed.

Dosage. Dried extracts of the anterior lobe, of the posterior lobe, and of the whole gland may be administered by the mouth in large quantities—as much as one hundred grains have been given three times a day. The dose should be regulated by the requirements of the case and the effects produced.

Infundibulin, when injected intramuscularly, must be given with caution: the quantity administered may vary from 0·25 to 1·0 c.c. In primary and secondary uterine inertia the amount of the first injection should never exceed 0·5 c.c., for a larger quantity may have too violent an action in a susceptible woman.

GENERAL INDICATIONS FOR ADMINISTRATION

The most notable effects and benefits of pituitary medication are obtained in those cases in which a rapid result is desirable. In such circumstances the extract used is that made from the pars posterior, and its action is exerted upon all the unstriped muscle-tissues of the body. These effects have been described and illustrated in the physiological section of this work, so they need not be rediscussed here.

Following physiological investigations[1] infundibulin was first

[1] Bell, W. Blair, and P. Hick, *Brit. Med. Journ.*, 1909, i, 777. (Received for publication Sept. 1908.)

employed, in the treatment of shock, uterine atony and intestina paresis in 1908[1]. Since that time innumerable papers on this subject have appeared, and a few further indications for the use of infundibulin when an immediate effect is required have been suggested. As we shall see, the therapeutical uses of the extract made from the pars anterior are not so well defined.

The indications for the administration of pituitary extracts may be divided into the following categories, according to the requirements of the case, although sometimes more than one action is indicated, especially when antagonistic and metabolic effects are required.

A. For pressor effects on :
   (1) the circulatory system ;
   (2) the uterus ;
   (3) the alimentary tract ;
   (4) the urinary system ;
   (5) the spleen.

B. For supplementary effects.

C. For antagonistic and metabolic effects.

GENERAL CONTRAINDICATIONS

Infundibulin should not be administered, except possibly with great caution and in small doses, in the following circumstances.

When there have been signs of respiratory failure during an operation an injection of infundibulin may bring about a fatal issue.

Owing to the action of this extract on the blood-pressure it is entirely contraindicated in cases of heart-disease which is not compensated; even when there is compensation none but the smallest doses are admissible. Likewise, this preparation is contraindicated in any condition associated with high arterial tension.

Infundibulin should not be used after operations involving intestinal repairs, or anastomoses, lest the suture lines be torn asunder by violent peristalsis.

Infundibulin is absolutely contraindicated for the stimulation of labour when there is disproportion between the fœtal head and the maternal pelvic measurements. So, too, all forms of fœtal impaction or obstructed labour, and many forms of abnormal presentations form definite contraindications to its use.

[1] Bell, W. Blair, *Brit. Med. Journ.*, 1909, ii. 1609.

§ ii. EFFECTS PRODUCED BY PITUITARY EXTRACTS

PRESSOR EFFECTS OF INFUNDIBULIN

CIRCULATORY SYSTEM

It is worthy of note that after the injection of a full dose of infundibulin the patient becomes blanched owing to the contraction of the superficial arterioles. This phenomenon may alarm unnecessarily an inexperienced nurse.

Shock

Infundibulin may be used either as a prophylactic measure for the prevention of shock, or as a remedial agent when shock is present.

This is not the place to discuss the various theories concerning the causation of shock[1]. All surgeons know that the main factors are trauma and loss of blood, alone or together, and toxæmia; and it is generally agreed that a low blood-pressure is present. The evidence on these points is quite unassailable; and one has only to watch the effect on the blood-pressure of an anæsthetic, combined with loss of blood and trauma due to operative procedures, to be convinced that the maintenance of a satisfactory blood-pressure and fluid-compensation are of the greatest importance in the treatment of shock. And it will be evident that if there have been a considerable loss of blood no attempt should be made to raise the blood-pressure until a corresponding, or greater, amount of fluid has been passed into the blood-stream by transfusion. It cannot, therefore, be too strongly emphasized

[1] Since this section was written a memorandum of the Medical Research Committee has been published (*Brit. Med. Journ.*, 1917, i, 381). The views expressed therein in regard to treatment coincide very closely with those described here.

that although infundibulin is most valuable in the prophylaxis of shock, and in maintaining the blood-pressure after the transfusion of saline solution, this preparation must not be regarded as a specific remedy for the treatment of shock which follows loss of blood, unless that loss be made good before the patient is moribund.

It is probable that at the present time no case should die of shock after operation. Continuous subcutaneous saline infusions during protracted operations, and an injection of 1 c.c. of a 20 per cent. extract of the pars posterior before the patient leaves the table, will usually enable her to be returned to bed in good condition—provided, of course, that the ordinary precautions in the matter of warmth, and of rapidity and gentleness in operating have been taken into account.

No doubt the administration of infundibulin alone after an extensive operation is of considerable value, provided no great quantity of blood has been lost, nor too great evaporation have occurred from the peritoneum[1]. In the shock, also, that supervenes on an accident in which a limb, for instance, is badly crushed or injured without the loss of blood, infundibulin is most valuable to restore the vasomotor tone.

One of the great advantages of infundibulin is the length of time its action is maintained. I have observed the blood-pressure to be beneficially affected for as long as eight hours after a single administration. This has important bearings, not only in regard to the advantage that accrues to the patient from this persistent action, but also in that it is both useless and inadvisable to repeat the administration of this substance within too short a period, for if this be done a fall rather than a rise in blood-pressure is produced. My own rule has been not to repeat a dose for at least two hours, at the end of which time a further pressor effect may be obtained.

Collapse

In collapse, due to sudden failure of the heart's action, rather than a general vasomotor paresis, I have come to regard infundibulin as useful only when employed in very small doses (0·25 c.c.) and given intravenously in saline. Elliott[2] and others consider

[1] I have for many years employed a rubber sheet instead of a gauze pack in order to avoid irritation of the peritoneum and evaporation therefrom.

[2] Elliott, T. R., *Practitioner*, 1915 (*Special number*), 123.

that suprarenin is more valuable as a cardiac restorative in these circumstances. At the same time the fatal combination of chloroform and suprarenin must not be forgotten.

Sepsis

In sepsis of a serious character, such as may occur with appendicitis or puerperal infection, infundibulin is of the very greatest value.

I have used it for the treatment of these conditions for some years, and am convinced that many lives have been saved by the administration of 0·5 c.c. of this preparation intramuscularly twice daily, so long as acute symptoms are present. Infundibulin has also been used with benefit in typhoid fever.

Sepsis produces a profound depression of the blood-pressure, and loss of tone of the involuntary musculature generally. This is probably the result of lesions in the suprarenal medulla, which I have found in experimentally produced infections in guinea-pigs. The administration, therefore, of infundibulin counterbalances any temporary failure in the suprarenal secretion. It has already been mentioned that there is naturally increased activity in the pituitary—unless necrosis occur—as the result of infections.

Serum-sickness

In this condition, in which a state of shock may be produced, the intramuscular injection of infundibulin is of great advantage.

In addition to the elevation of the general blood-pressure, the administration of infundibular extract is of considerable value in preventing the development of the urticarial weals which may form so distressing a feature of serum-sickness. This beneficial result is probably due to the constriction of the arterioles and the prevention of dilatation. That there is little or no exudation at the site of the lesion, but rather a condition of temporary vasodilatation, is shown by the rapidity with which a weal disappears from one spot and appears elsewhere.

It is possible that infundibulin would be useful in the treatment of angioneurotic œdema—a similar condition—but I am not aware of any observations on the subject.

Menopausal flushings

These are due to sudden variations in the blood-pressure—probably the result of an irregular action of the thyroid. I have found that if the blood-pressure be maintained at a slightly higher level than normal by the administration of infundibulin this discomforting phenomenon can be entirely suppressed or made endurable.

It is, however, advisable to combine the administration of infundibulin—given orally—with calcium lactate, and eventually to withdraw the extract partly or entirely in favour of the calcium salt, which is a less drastic vasomotor tonic.

Spasmodic asthma

Infundibulin is sometimes of great value in relieving the distress of an acute attack of asthma.

There can be no doubt that when relief is obtained the result is due to the production of vasoconstriction of the pulmonary arterioles. Apparently, however, this beneficial action is somewhat uncertain in the case of infundibulin. The principle of treatment on which this action is based was first demonstrated in the case of ergot[1], and later by the use of suprarenin[2].

Asthenia

In chronic asthenic conditions associated with a low blood-pressure the tonic effect of the extract of the posterior lobe is most beneficial. In these circumstances it is advisable to give either the extract of the whole gland in five-grain doses three times a day, or an extract of the pars posterior in doses of two grains twice a day.

A considerable amount of work has been done on this aspect of the subject by Rénon and Delille[3], by Musser[4] and others.

[1] Bell, W. Blair, *Edin. Med. Journ.*, 1899, xlviii, 339.
[2] Meulangracht, E., *Ugeskr. f. Loeger*, Copenhagen, 1913, lxxv, 1847.
[3] Rénon, L., and A. Delille, *Bull. gen. d. Ther.*, 1907, cliii, 178.
[4] Musser, J. H., *Amer. Journ. Med. Sci.*, 1913, cxlvi, 208.

UTERUS

Since the discovery of the pressor action of the extract of the pituitary, and of the pars posterior in particular, it is probable that the extract has been used in physiological laboratories for the comparative testing of the pressor substances. Thus we find that Dale[1] illustrated the action of an extract of the pars posterior on the uterus in a paper relating to the action of ergot; but he did not suggest the possibility of its clinical application.

In 1908 we[2] studied experimentally the action of infundibulin on the uterus, and applied our results to clinical practice[3].

Obstetrical uses

Among the vast number of papers concerning the obstetrical uses of infundibulin that subsequently appeared it will be sufficient to call attention to those of Foges and Hofstätter[4], Frankl-Hochwart and Fröhlich[5], Hofbauer[6], Schmid[7], Jaeger[8], Watson[9], and Madill and Allan[10].

The remarkable position that infundibulin has come to occupy in obstetrical practice has been the subject of frequent comment. Watson[9], writing in 1913 of the value of pituitary extract in obstetrics, introduces his subject with the following words: "It seldom happens that a new drug or remedy comes into universal use in such a short space of time as has been the case with pituitary extract in obstetrical practice. Since it was first used . . . in 1909 it has been employed in practically every obstetrical clinic throughout this continent, and in Britain and Europe."

This very popularity has led to extravagant claims being made in regard to the virtues of this extract. More than one writer has stated that forceps are no longer required in difficult

[1] Dale, H. H., *Journ. Physiol.*, 1906, xxxiv, 163.

[2] Bell, W. Blair, and P. Hick, *Brit. Med. Journ.*, 1909, i, 777.

[3] Bell, W. Blair, *Brit. Med. Journ.*, 1909, ii, 1609.

[4] Foges, A., and R. Hofstätter, *Zentralbl. f. Gynak.*, 1910, xxxiv, 1500.

[5] Frankl-Hochwart, L. v., and A. Fröhlich, *Arch. f. exper. Pathol. u. Pharmakol.*, 1910, lxiii, 347.

[6] Hofbauer, J., *Zentralbl. f. Gynak.*, 1911, xxxv, 137.

[7] Schmid, H. H., *Gynak. Rundschau*, 1911, v, (Reprint).

[8] Jaeger, F., *Munch. Med. Woch.*, 1912, lix, 297.

[9] Watson, B. P., *Canad. Med. Assoc. Journ.*, 1913, iii, 739.

[10] Madill, D. G., and R. M. Allan, *Surg. Gynæcol. and Obstet.*, 1914, xix, 241.

labour. Such statements are not only ridiculous, but positively dangerous. Properly used, infundibulin is analeptic; improperly employed it may be catastrophic.

The indications for the use of infundibulin in pregnancy, parturition and the puerperium, are now well defined.

The dosage of infundibulin in *parturition* is a matter of great importance. The quantity injected in the first instance should never exceed 0·5 c.c. An even smaller quantity may advantageously be used in these circumstances.

Induction of labour.—Although abortion has never been produced by the administration of infundibulin, there is no doubt that labour may occasionally be induced towards the end of the period of gestation by repeated intramuscular injections.

Stern[1], Fries[2], Hofbauer[3], Goebel[4], Krakauer[5], Stolper[6], Hager[7], Herzberg[8], Watson[9] and others, have reported successful results, and I have myself on several occasions induced premature labour by the use of the extract alone. On the other hand, failure to induce labour has been very common[3, 10, 11].

Impressed with these facts, and noting the remarkable action of this extract in cases of primary uterine inertia, I came to the conclusion that infundibulin not only augments contractions in the expulsively contracting, or potentially contracting, uterus, but also *sensitizes* the non-contracting musculature which thereafter responds readily to mechanical stimuli, and as a result contracts expulsively in a physiological manner after dilatation of the cervix or mechanical irritation with bougies[12].

Labour may, then, be induced in the following manner, within a few weeks of the full term, or in postmaturity of the fœtus.

The patient is confined to the house, not necessarily to bed,

[1] Stern, R., *Berl. Klin. Woch.*, 1911, xlviii, 1459.
[2] Fries, H., *Munch. Klin. Woch.*, 1911, lxviii, 2438.
[3] Hofbauer, J., *Munch. Med. Woch.*, 1912, lix, 1210.
[4] Goebel (no initial in original), *Munch. Med. Woch.*, 1912, lix, 1669.
[5] Krakauer (no initial in original), *Berl. Klin. Woch.*, 1912, xlix, 2317.
[6] Stolper, L., *Zentralbl. f. Gynak.*, 1913, xxxvii, 162.
[7] Hager, W., *Zentralbl. f. Gynak.*, 1913, xxxvii, 304.
[8] Herzberg, S., *Deut. Med. Woch.*, 1913, xxxix, 207.
[9] Watson, B. P., *Canad. Med. Assoc. Journ.*, 1913, iii, 739.
[10] Hirsch, E., *Munch. Med. Woch.*, 1912, lix, 984.
[11] Nagy, T., *Zentralbl. f. Gynak.*, 1912, xxxvi, 300 and 826.
[12] Bell, W. Blair, *Proc. Roy. Soc. Med.* (*Obstet. and Gynæcol. Sect.*), 1915, viii, 71.

and 1 c.c. of infundibulin (20 per cent.) is injected intramuscularly at night and in the morning for three days. It is advisable that the patient should lie down for an hour after each injection. At the end of this period two or more bougies are inserted into the uterus in the ordinary way, immediately after the last injection has been given. If labour does not commence within twelve hours another intramuscular injection of infundibulin is administered.

In a somewhat limited experience I have not known the induction of labour to be delayed for so long as twenty-four hours after the insertion of the bougies; yet it is well known how uncertain is the action of bougies alone. A larger experience may, of course, somewhat modify my present opinion of the celerity of this method of induction.

I have said that preliminary treatment with infundibulin should be carried out for three days before the bougies are inserted, but it should be remembered that labour may be induced before this time, and so render the insertion of bougies unnecessary. On the other hand, it may be essential that the administration of infundibulin be continued for a longer preparatory period than three days. The obstetrician can decide the necessity, or otherwise, of the continuance of the administration of infundibulin by observing the state of the uterus. The effect of infundibulin on the uterus before parturition is very striking: the eventual sensitization of the musculature is such that the slightest stimulus, such as gentle manual kneading, causes the uterus to spring to attention—that is, to contract firmly. This state must be produced before the bougies are inserted.

It has been suggested[1] that the effect of infundibulin on the pregnant uterus may be used to distinguish labour pains from other pains occurring in the normal course of pregnancy. But it is doubtful if such a test would be reliable in view of the action of infundibulin on the intestine.

Primary uterine inertia.—The precise cause of the uterine contractions in labour is still unknown, although all the evidence at our disposal points to the presence of some pressor substance in the blood which sensitizes the uterus to such an extent that

[1] Benthin, W., *Zeitschr. f. Geb. u. Gynak.*, 1912, lxx, 60.

the fœtus and placenta play the part of foreign bodies stimulating the musculature to expulsive contractions. And it is, no doubt, some deficiency in the sensitizing and pressor substance or substances that is responsible for the condition known as primary uterine inertia.

It is important that primary uterine inertia should be recognized *before labour*. This is not difficult, owing to the flabby state of the uterus which is indifferent to stimulation, to the low general blood-pressure, and to the subnormal calcium index in the blood[1]. Such a state should be treated by the oral administration of calcium salts and the dried extract of the posterior lobe (gr. v *ter in die*) or of the whole gland (gr. xx *ter in die*).

It is an interesting fact, which will come under our notice again later, that infundibulin not only directly sensitizes the uterus, but also influences beneficially the retention of calcium salts in the blood and tissues of the body. I have seen women with bad obstetrical histories in regard to primary uterine inertia, go through easy and rapid labours after treatment in the manner described.

When labour has commenced and the uterine contractions are feeble and ineffective, if there be no contraindications, such as disproportion between the maternal and fœtal measurements, malpositions or obstructed labour, infundibular extract (0·5 c.c.) should be injected intramuscularly. As a rule, the contractions are increased in force and frequency within a few minutes, and the character of the contractions is entirely physiological and rhythmical (fig. 187).

Further injections may be administered if necessary after intervals of a few hours.

Madill and Allan[2], in their series of cases at the Rotunda Hospital in Dublin, administered infundibulin for primary uterine inertia to four primigravidæ and nine multiparæ. The first injection was given to the former when the os uteri was one half to three quarters dilated and after the patient had been in labour for an average time of twenty hours. The subsequent duration of labour was on an average only two hours. In the cases of multiparæ, who had been in labour for an average time of thirteen hours, the first injection was given when the

[1] Bell, W. Blair, *Proc. Roy. Soc. Med.* (*Obstet. and Gynæcol. Sect.*), 1915, viii, 71.

[2] Madill, D. G., and R. M. Allan, *Surg. Gynæcol. and Obstet.*, 1914, xix, 241.

os was one quarter dilated. The subsequent average period of labour in these cases was only forty minutes.

These authors, like Strassmann[1] and most other observers,

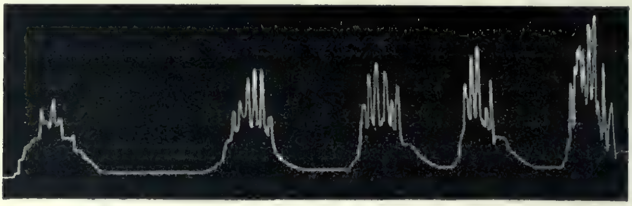

FIG. 187.

Kymograph-tracing showing the increase in regular physiological uterine contractions during labour after an intramuscular injection of 0·6 c.c. of infundibulin in primary inertia. (*Malinowsky.*)

found that the placenta is expelled in about fifteen minutes—a shorter period than is usual in normal labour.

Secondary uterine inertia.—It is probable that, other conditions being suitable, the use of infundibulin in secondary uterine inertia—a very common condition—far exceeds all other applications of the effect of this preparation on the uterus.

FIG. 188.

Kymograph-tracing showing the resumption of regular physiological uterine contractions after an intramuscular injection of 1·2 c.c. of infundibulin in secondary inertia. (*Malinowsky.*)

In these circumstances the head is usually in the pelvis, and the labour 'pains' have either ceased or have diminished in frequency and force. Following the intramuscular injection of 0·5 c.c. of infundibular extract there is, almost immediately, re-establishment of rhythmical and forcible uterine contractions (fig. 188). This is illustrated by Madill and Allan[2], who have published a series of charts in their paper to show the duration

[1] Strassmann, P., *Zentralbl. f. Gynak.*, 1912, xxxvi, 438.

[2] Madill, D. G., and R. M. Allan, *Surg. Gynæcol. and Obstet.*, 1914, xix, 241.

and force of the 'pains' (fig. 189). In these charts the effect of infundibulin on the fœtal heart is recorded. Similar charts had previously been published by Jaeger[1].

The children born after the use of infundibular extract are sometimes cyanosed and have a slow heart-action[1, 2, 3, 4, 5].

It is possible that the condition of the fœtal heart is caused by the infundibulin circulating in the maternal blood, and that the cyanosis is due to the rapidity of recurrence and to the force of the uterine contractions.

Anæsthetics have but little effect in diminishing the contractions produced by infundibulin[5]; nor do opium derivatives interfere with its action—Schmid[6], indeed, advises that pantopon be used in conjunction with infundibulin as a routine procedure. I have found that omnopon, or scopolamin and morphin ('twilight-sleep'), may very advantageously be combined with infundibulin, in order to shorten the period of labour.

Placenta prævia.—In this condition infundibulin appears to have been widely used, and many observers[5, 6, 7, 8, 9, 10, 11,] who have employed it—usually in conjunction with rupture of the membranes, hydrostatic bags, vaginal packing, or with turning—are convinced of its value in safely effecting delivery, provided the other conditions are favourable for its administration.

It will be obvious that the best effect of infundibular extract will be obtained when the placenta prævia is not central; nevertheless, good results have been obtained even when the placenta has been more or less centrally situated over the os uteri.

Accidental hæmorrhage.—In the absence of definite contra-indications, and after rupture of the membranes, an intramuscular

[1] Jaeger, F., *Munch. Med. Woch.*, 1912, lix, 297.
[2] Hofbauer, J., *Zentralbl. f. Gynak.*, 1911, xxxv, 137.
[3] Fischer, O., *Zentralbl. f. Gynak.*, 1912, xxxvi, 15.
[4] Lieven, F., *Zentralbl. f. Gynak.*, 1913, xxxvii, 337.
[5] Madill, D. G., and R. M. Allan, *Surg. Gynæcol. and Obstet.*, 1914, xix, 241.
[6] Schmid, H. H., *Gynak. Rundschau*, 1911, v, (Reprint).
[7] Bell, W. Blair, *Brit. Med. Journ.*, 1909, ii, 1609.
[8] Hofbauer, J., *Munch. Med. Woch.*, 1912, lix, 1210.
[9] Watson, B. P., *Canad. Med. Assoc. Journ.*, 1913, iii, 739.
[10] Studeny, A., *Wien. Klin. Woch.*, 1911, xxiv, 1766.
[11] Gall, M. E., *Zentralbl. f. Gynak.*, 1913, xxxvii, 77.

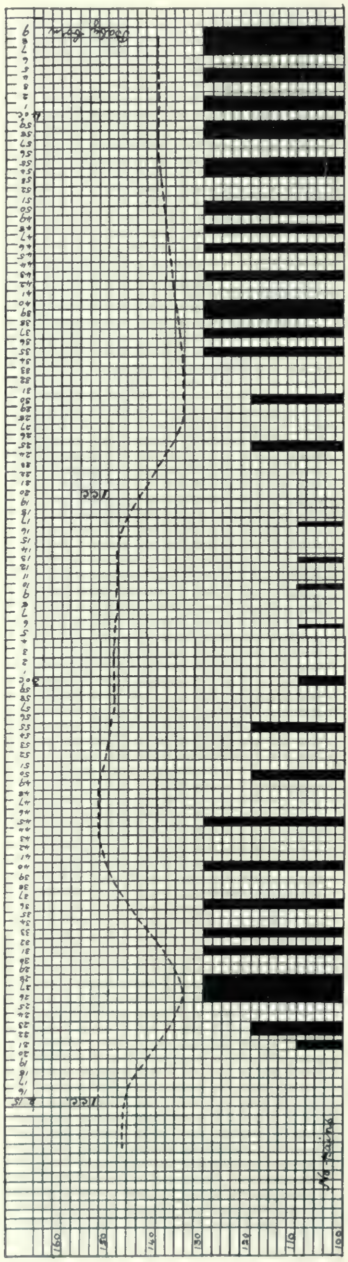

Fig. 189.

Chart showing the effect of infundibulin on the uterine contractions (vertical black lines), and on the fœtal heart (dotted line), in a case of secondary uterine inertia in a primigravida. The os was fully dilated and the head in the pelvis. A column from 100–110 represents a weak contraction, one from 110–120 a moderately strong contraction, and a column from 120–130 a powerful contraction. Each vertical space represents one minute. (*Madill and Allan.*)

injection of infundibulin may form a valuable adjunct to other treatment, even if it be not entirely effectual in itself.

Postpartum hæmorrhage.—Infundibulin, owing to its rapid action on the uterus after intramuscular injection, is very valuable in postpartum hæmorrhage[1,2,3]. At the same time, since the contractions produced by this preparation in the uterus are rhythmical in character, its action is probably not always so lastingly effective as the preparations of ergot which produce tetanic spasm of the uterine musculature. But it has been found that the action of ergot is increased by simultaneous or previous sensitization of the uterus with infundibulin; consequently it is advisable to use the two drugs in combination for the treatment of hæmorrhage occurring *post partum.*

Cæsarean section.—Infundibulin has been extensively used with most beneficial results[1,2,3,4,5]. The injection may be made in the maternal muscles during the operation, or directly into the uterine muscle after the uterus has been emptied. In my experience the former method is the better, for if the extract be injected directly into the uterus, that organ may become so tightly contracted that it is difficult to suture the wound in the muscle-wall.

Acute subinvolution.—It has been found that when there is no such cause for subinvolution as fibromyomata uteri or other gross pathological lesion, the condition can be effectually treated by the daily administration of infundibulin. It is, however, in these cases advisable also to prescribe calcium salts during the treatment with pituitary extract and after this extract has been discontinued.

Abortion.—Infundibulin is ineffectual in causing the expulsion of the ovum and placenta in the first half of the period of gestation. Indeed, the uterus is generally found to contract down on and grasp the embryo and placenta, and the cervix to be

[1] Bell, W. Blair, *Brit. Med. Journ.*, 1909, ii, 1609.
[2] Foges, A., and R. Hofstätter, *Zentralbl. f. Gynak.*, 1910, xxxiv, 1500.
[3] Schmid, H. H., *Gynak. Rundschau*, 1911, v, (Reprint).
[4] Hofbauer, J., *Zentralbl. f. Gynak.*, 1911, xxxv, 137.
[5] Herzberg, S., *Deut. Med. Woch.*, 1913, xxxix, 207.

tightly closed[1, 2]. If, however, the uterus have been emptied, the administration of infundibulin is very valuable, when injected intramuscularly daily for a few days to induce proper involution.

Bad effects stated to have followed the use of infundibulin in obstetrical practice

A few cases have been recorded in which the administration of infundibulin is said to have produced rigidity of the cervix during labour [3, 4, 5]. This must be a most unusual circumstance, and the accounts of these cases are somewhat unsatisfactory.

Hour-glass contraction[6] of the uterus after the birth of the child, and postpartum hæmorrhage[7] following injections of infundibulin have been recorded. There can be no doubt that both these occurrences would be likely if the placenta were

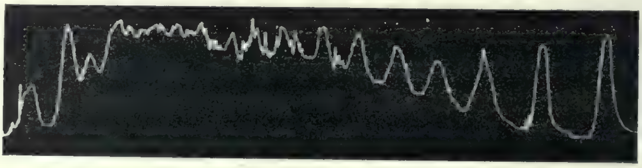

FIG. 190.

Kymograph-tracing showing tetanic uterine contractions of short duration, followed by powerful rhythmical contractions after an intramuscular injection of infundibulin in secondary uterine inertia. (*Malinowsky.*)

unduly retained. To avoid such accidents, when infundibulin has been given during labour, it is advisable to express the placenta at the end of twenty minutes after the birth of the child, if it have not already been expelled.

Rupture of the uterus, which is quite avoidable and is a serious reflexion on the accoucheur, has followed the administration of infundibulin *when there has been obstruction to delivery.* A certain number of these disasters is on record, and several have been privately communicated to me. I myself have never seen such a mishap.

[1] Hamm, A., *Munch. Med. Woch.*, 1912, lix, 77.
[2] Watson, B. P., *Canad. Med. Assoc. Journ.*, 1913, iii, 739.
[3] Mackenrodt (no initial in original), *Zentralbl. f. Gynak.*, 1911, xxxv, 679.
[4] Heil, K., *Zentralbl. f. Gynak.*, 1912, xxxvi, 1398.
[5] Rieck (no initial in original), *Munch. Med. Woch.*, 1912, lix, 816.
[6] Glass, R. L., *Brit. Med. Journ.*, 1914, ii, 72.
[7] Levinson, W. E., *Brit. Med. Journ.*, 1914, ii, 1046.

Malinowsky[1] states that he has seen tetanic spasms (fig. 190) in the uterus lasting for one quarter of an hour when infundibulin has been injected before the dilatation of a rigid cervix; but he states that the spasms disappeared as labour advanced.

I have already referred to the slight bad effects that have occasionally been observed in regard to the child.

Contraindications to the use of infundibulin in obstetrical practice

If the mother be the subject of disease of the heart or kidneys, especially with arteriosclerosis, this preparation is dangerous and may be fatal.

Madill and Allan[2] record a case of heart-disease in which infundibulin was administered for uterine inertia. As a result of this treatment the patient collapsed, and was with difficulty resuscitated with stimulants.

Hauch and Meyer[3], and Brammer[4], also, advise against the use of infundibulin if the mother suffer with cardiac or renal disease; and the former also call special attention to the fact that this extract should not be used in the presence of eclamptic manifestations with a high blood-pressure.

It is only right, however, to state that certain writers[5, 6] state that kidney-disease is not a contraindication to the use of infundibulin. As a matter of fact, the state of the blood-pressure should afford a clue as to the safety or otherwise of the administration of the extract in these circumstances.

Owing to the high blood-tension usually found in eclampsia I have never felt justified in using infundibulin to induce or terminate labour in these circumstances. Krakauer[7] and others have, however, employed the extract for these purposes.

With regard to the local conditions—fœtal and maternal—there are many important contraindications to the use of infundibulin.

[1] Malinowsky, M., *Zentralbl. f. Gynak.*, 1912, xxxvi, 1425.

[2] Madill, D. G., and R. M. Allan, *Surg. Gynæcol. and Obstet.*, 1914, xix, 241.

[3] Hauch, E., and L. Meyer, *Hopitalstidende*, Copenhagen, 1912, lv, 389.

[4] Brammer, M., *Hopitalstidende*, Copenhagen, 1912, lv, 389.

[5] Stern, R., *Zentralbl. f. Gynak.*, 1911, xxxv, 1113.

[6] Gussew, W., *Zentralbl. f. Gynak.*, 1912, xxxvi, 1755.

[7] Krakauer (no initial in original), *Berl. Klin. Woch.*, 1912, xlix, 2317.

In malpositions of the fœtus, such as the oblique and the persistent mentoposterior positions, which render it impossible for the child to be born unless there be an alteration of the attitude, the uterus may be ruptured by the violent contractions induced by this oxytocic.

So, too, when there is undue disproportion between the fœtal head and the maternal passages—*a state that exists to some extent in all normal primigravidæ*—or there is obstructed labour from any cause whatsoever, infundibulin should not be given to augment the force of the uterine contractions lest rupture of the uterus occur; and in elderly primigravidæ where the rigid parts may be lacerated the drug must be used with caution.

Although infundibulin has been employed successfully in minor degrees of obstruction and in some malpositions, such temerity on the part of the accoucheur does not detract from the fact that its use in such circumstances is highly dangerous.

From these remarks it will be evident that in experienced hands, when the indications and contraindications are duly considered, no bad effects either to the mother or child are likely to follow.

Gynæcological uses

In *menorrhagia* due to increased or irregular activity in the thyroid and ovaries—such as is seen at puberty and the menopause—intramuscular injections of infundibulin are invaluable. Likewise, in those cases in which there is menorrhagia with intrauterine clotting of the menstrual blood as the result of decreased muscular tone in the uterus and involuntary muscular system generally, infundibulin may bring about a rapid improvement.

In these cases it is advisable to administer the infundibular extract during menstruation only and to prescribe calcium salts[1] during the menstrual intervals.

Apart from excessive menstruation infundibulin will, temporarily, at any rate, control bleeding—due to almost any cause—from the corpus uteri[2] owing to its action on the muscle-fibres.

[1] Mist. calcii lactatis recentis (C & A): ℥i om. nocte.

[2] Bab, H., *Munch. Med. Woch.*, 1911, lviii, 1554.

ALIMENTARY TRACT

Infundibulin may be used to prevent and to relieve acute *paralytic distension of the stomach and intestine* which is sometimes seen after abdominal operations. We first called attention to this in 1909[1,2]. Since that time many observers have recorded their experiences[3,4,5]; and the preparation is now very generally used in preference to eserine and the other drugs previously employed to stimulate peristalsis.

The contraindications already mentioned, namely, cardiac disease, renal disease associated with a high blood-pressure, and intestinal suture, prohibit the use of infundibulin in the circumstances under consideration; and this is more especially the case since to secure pronounced peristalsis large doses are necessary—that is to say, 1 to 2 c.c. of the extract. In intestinal paresis, or distension, following abdominal operations, I have found, however, that 1 c.c. of infundibulin is always enough if a turpentine enema be given ten minutes after an intramuscular injection of the extract.

It is probable, too, that the best results are obtained with acute gastric distension if the stomach be washed out ten minutes after an intramuscular injection of infundibulin.

In chronic constipation the continued oral administration of an extract of the whole gland or of infundibulin has given good results in many cases in which the constipation has been due to loss of tone in the intestinal musculature[6].

URINARY SYSTEM

Kidneys.—As we have seen, Magnus and Schäfer[7] claim that the extract of the pars nervosa has a definite diuretic effect, and there is no doubt that this preparation has been extensively used for producing diuresis. Hofstätter[8] states that postoperative anuria is invariably relieved by injections of infundibulin.

1 Bell, W. Blair, and P. Hick, *Brit. Med. Journ.*, 1909, i, 777.
2 Bell, W. Blair, *Brit. Med. Journ.*, 1909, ii, 1609.
3 Bidwell, L., *Clin. Journ. Lond.*, 1911, xxxviii, 351.
4 Houssay, B. A., and J. Beruti, *Presse Médicale*, 1913, xxi, 613.
5 Moynihan, B., *Abdominal Operations*, 1914, i, 63.
6 Musser, J. H., *Amer. Journ. Med. Sci.*, 1913, cxlvi, 208.
7 Magnus, R., and E. A. Schäfer, *Journ. Physiol.*, 1901, xxvi, ix.
8 Hofstätter, R., *Wien. Klin. Woch.*, 1911, xxiv, 1702.

In my own experience I have not often noted clinically any very definite diuresis in patients who have had injections of infundibulin regularly twice a day for some days. Nevertheless, in the prevention and treatment of shock, in which state the secretion of the kidneys is diminished, infundibulin may act indirectly; and this applies especially to postoperative anuria.

Bladder.—Frankl-Hochwart and Fröhlich[1] have shown that injections of infundibulin stimulate the musculature of the bladder, which subsequently reacts more energetically to stimulation of the hypogastric nerves. As a result of their experiments these investigators have recommended the clinical use of the extract in paresis of the bladder.

In my experience the action of even large doses of infundibulin on the bladder is somewhat uncertain; and in postoperative paresis I have never seen the bladder emptied unless the injection were given when the bladder was fully distended, and even in these circumstances the extract often fails to produce the desired effect.

I have, therefore, adopted the following procedure, which sometimes succeeds. An intramuscular injection of infundibulin is given when the bladder is distended. If no result is produced, a catheter is passed and a few ounces are allowed to flow through it; the catheter is then withdrawn, and after this the patient may continue to pass urine normally.

MAMMARY GLANDS

Infundibulin, when intravenously injected, produces a rapid flow of milk from the incised lactating breast, as already demonstrated; and there has been much discussion as to whether this is an expulsive or a true galactogogue effect.

The observations of Heaney[2] and others on the human subject leave no room for doubt that any increased supply of milk obtained is temporary, and is usually followed by a decrease; consequently it is certain that infundibulin is of little use

[1] Frankl-Hochwart, L. von, and A. Fröhlich, *Arch. f. Exper. Pathol. u. Pharmakol.*, 1910, lxiii, 347.

[2] Heaney, N. S., *Surg. Gyn. and Obstet.*, 1913, xvii, 103.

therapeutically as a galactogogue when the secretion of milk is deficient.

The employment of infundibulin in threatened mammary abscess has been suggested, but it is difficult to understand how an abscess could be aborted by this means.

SPLEEN

I am not aware of any cases recorded in the literature in which infundibulin has been used to produce contractions in the muscular tissue of the spleen.

My colleague R. J. M. Buchanan, however, has treated successfully a serious case of splenomegaly by the oral administration of an extract of the whole gland.

SUBSTITUTIONAL AND SUPPLEMENTARY EFFECTS OF PITUITARY EXTRACTS

It is probable that true substitutional effects are never observed in the human subject ; that is to say, total destruction or removal of the gland is not compatible with life, even though substitution-therapy be practised. We are, therefore, only concerned clinically with the supplementary effects of pituitary extracts.

We have seen that insufficiency of the pituitary may produce a very obvious train of symptoms giving rise to the syndrome *dystrophia adiposogenitalis ;* yet there is little doubt that minor degrees of insufficiency of a temporary or permanent character are by no means uncommon, just as are the minor and less easily recognized insufficiencies of the thyroid.

It will be remembered, also, that Cushing[1] has found that the subnormal temperature associated with the high degrees of pituitary insufficiency can be elevated by injections of an extract of the pars anterior, while the low blood-pressure is raised and the sugar-tolerance lessened by the administration of infundibulin ; consequently in such cases an extract of the whole gland is indicated.

The results of this method of treatment are not very good. Cushing[1] after a large experience found that the hypodermic administration of an extract of the whole gland occasionally gave good *temporary* results. In one case, the patient became active mentally and physically, so the pituitary of a newly born infant, which died during birth, was grafted in the subcortical tissues of the temporal lobe of the patient with complete operative and therapeutical success. Nevertheless, it is difficult to estimate how far this excellent result was due to the effect of the grafted gland, for an hypophysial cyst had been evacuated a few weeks previously, although without any apparent benefit.

[1] Cushing, H., *The Pituitary Body and its Disorders*, **1912.**

In a case which came under my own notice in the year 1910, a man almost completely blind, and suffering from adiposity and genital atrophy with impotence, was treated with hypodermic injections of an extract of the pars anterior for a long time. Eventually he recovered his potency and impregnated his wife who gave birth subsequently to a full-term child.

From the evidence at our disposal it appears that supplementary medication should be combined with surgical treatment of the pituitary lesion; and, if permanent benefit is to accrue, that implantation may offer the most convenient method of meeting the deficiency of pituitary secretion.

In the minor degrees of insufficiency the results obtained have been fairly good. Hofstätter[1] claims to have had pronounced success in the alleviation of amenorrhœa associated with adiposity; but in some cases thyroid extract was also given. Hofstätter's method of treatment was by hypodermic medication, and it was found that coincidental oral administration was of advantage. In only about a third of the cases could menstruation be preserved by frequent administration of the extract. Fromme[2] has obtained similar results. Williams[3], also, has reported an interesting case of amenorrhœa which was successfully treated with pituitary extract. If, in this case, the drug was discontinued amenorrhœa was again in evidence.

In my own experience, chiefly of oral administration, the results have not been striking, although in a few patients scanty and infrequent menstruation has been induced. Most of the patients have complained bitterly of the severity of the headaches with which they suffered while taking the extract of the pars anterior.

It seems certain that, unless the arrest of menstruation is subject to treatment at an early period, genital atrophy may supervene, and render all prospect of beneficial treatment hopeless.

In no case have I observed any decrease in the adiposity of the subject after prolonged oral treatment with an extract of the whole gland, or with infundibulin, nor have I seen a permanent change in the carbohydrate-tolerance in these circumstances. It

[1] Hofstätter, R., *Zentralbl. f. Gynak.*, 1912, xxxvi, 1536.

[2] Fromme, F., *Zentralbl. f. Gynak.*, 1912, xxxvi, 1366.

[3] Williams, L., *Proc. Roy. Soc. Med.* (*Discussion*), 1914, vii, 37.

appears probable, therefore, that oral administration is of little value in supplementing diminished pituitary secretion.

Before we leave the consideration of the supplementary effects of pituitary extracts mention must be made of the fact that since physiologically the pars anterior is supplementary to the thyroid and ovaries—if we can so interpret the hyperplasia that occurs in this part of the pituitary as the result of the removal of these glands—the administration of the extract of the pars anterior has been suggested in primary hypoplasia of the ovaries and possibly of the thyroid. But such treatment is not indicated, for we know that in hypoplasia of the thyroid an extract of this organ itself effects a cure; and that in ovarian hypoplasia the administration of ovarian extract, which of itself is more or less inert, together with thyroid extract, may be beneficial[1].

Francesco[2], Barker and Hodge[3], and others consider that diabetes insipidus is due to insufficiency of the pars posterior of the pituitary, and find that injections of infundibulin arrest all the symptoms of this disease, including polyuria[4]. This somewhat paradoxical effect still awaits explanation.

[1] Bell, W. Blair, *The Sex Complex*, 1916; *The Disorders of Function: The Neu System of Gynæcology*, 1917.

[2] Francesco, F., *Gaz. d. Osp. e. d. Clin. Milan*, 1913, xxxiv, 1127.

[3] Barker, L. F., and M. Hodge, *Bull. Johns Hopk. Hosp.*, 1917, xxxiii, 355.

[4] Compare with pp. 109 and 177.

ANTAGONISTIC AND METABOLIC EFFECTS OF PITUITARY EXTRACTS

In the correlation of effects produced by the hormonopoietic organs we find that antagonistic and metabolic as well as supplementary actions are concerned ; so it is possible to utilize extracts of the pituitary to combat hyperplasia in some and hypoplasia in other organs, and to counteract abnormal metabolic states that have been produced by these conditions. Nevertheless, our knowledge on these matters is still most elementary, and the extracts of the pituitary are used almost empirically for the purposes indicated.

It is, of course, impossible to separate and to distinguish the direct action of an organ of internal secretion upon the metabolism from the effects of its action on another member of the hormonopoietic system and the resulting total effect on the metabolism. The fact remains, however, that, should the antagonism of the remedial agent succeed, the effect is seen not only in the metabolism but in the lessened activity of the organ of internal secretion whose excessive activity has been restrained.

Hyperthyroidism.—The extract of the posterior lobe may be used in the treatment of hyperthyroidism. We know that thyroid secretion lowers the blood-pressure and leads to the rapid excretion of lime salts. Infundibulin counteracts both these effects, and, like suprarenin, causes a rise in the blood-pressure and the storage of lime salts. At the same time, it often effects a diminution in the size of the thyroid gland and retrogression in the symptoms of hyperthyroidism, even to an improvement in, or the disappearance of, exophthalmos.

Osteomalacia.—This disease has usually been attributed to hyperplasia of the ovaries which are normally concerned in

the excretion of calcium from the maternal economy, and I have found hyperplasia of the ovarian interstitial cells in this disease[1]. Erdheim[2], however, has observed with osteomalacia hyperplasia of the parathyroids; but this is probably secondary, and is an antagonistic response to the ovarian hyperplasia. Bossi[3] believes that the osteomalacia is due to insufficiency of the suprarenal medullary secretion.

Whatever the truth may be concerning the causal factors in this disease, there is no doubt that the actual metabolic disturbance is an excessive excretion of calcium salts.

Formerly, the ovaries were removed in the treatment of this condition with satisfactory results in many cases. Then Bossi suggested the injection of suprarenal extract, also with satisfactory results.

A few years ago Kate Knowles, who was then in Kashmir, at my suggestion used infundibulin in the treatment of these cases with very good results, both in regard to the relief of pain, and the arrest of the disease.

Other conditions of imperfect calcium retention in the tissues.—As we have seen, much of the efficacy of continued medication of pituitary extracts is due to the effect of infundibulin, and possibly of the extract of the pars anterior, on the calcium metabolism.

This power of causing calcium retention in the tissues has been utilized by Klotz[4] in the treatment of rickets with some success.

Some years ago I was consulted in the remarkable case of a lady who suffered so severely from muscular and ligamentary weakness that she was quite unable to walk and even to hold a pen with which to write. This condition had followed an artificially produced menopause.

Prolonged treatment with infundibulin and calcium lactate led to a complete cure of the serious disabilities[5].

*   *   *   *

[1] Bell, W. Blair, *The Sex Complex*, 1916.

[2] Erdheim, J., *Sitz d. k. Akad. d. Wissench. Math.-naturw. Kl.*, Wien, 1907, cvvi, 3 *Abt*, 311.

[3] Bossi, L. M., *Zentralbl. f. Gynak.*, 1907, xxxi, 69.

[4] Klotz, R., *Munch. Med. Woch.*, 1912, lix, 1145.

[5] Simpson, A. Hope, *Liverp. Med. Chirurg. Journ.*, 1914, xxxiv, 357.

From the foregoing remarks concerning the therapeutical uses of pituitary extracts it will have been gleaned that much is entirely empirical if not purely speculative ; and that even in the present day our knowledge is only laid on sure foundations in regard to " the therapeutical value of the infundibular extract in shock, uterine atony, and intestinal paresis "—the title of the first clinical paper on the subject.

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